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Original Article

NOVEL QUERCETIN NANOEMULGEL OPTIMIZATION: GELLING AGENTS EVALUATION AND THE APPLICATION OF RESPONSE SURFACE METHODOLOGY

CHRISTOFORI MARIA RATNA RINI NASTITI[1*], RINI DWIASTUTI[1], FLORENTINUS DIKA OCTA RISWANTO[2]

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ABSTRACT

Objective: This current research aimed to examine the profile of a range of gelling agents by applying principal component analysis (PCA) based on certain physical properties and to develop a novel optimized nanoemulgel formulation containing quercetin (QUE).

Methods: A series of gelling agents with different concentrations were grouped and profiled by applying the PCA based on their viscosity and the spreadability. Based on the profile, one of the gelling agents was selected to be formulated in QUE nanoemulgel. The formulation of QUE nanoemulsion was then fabricated using a spontaneous emulsification method involving triacetin as the oil phase, a combination of Kolliphor® RH 40 and Transcutol® as the surfactant-cosurfactant system, and citrate buffer pH 6 as the aqueous phase. QUE nanoemulgel was fabricated by incorporating the gelling agent (sodium carboxymethylcellulose; Na CMC) into the nanoemulsion. The composition of Kolliphor® RH 40, Transcutol®, and Na CMC in the formulation was further optimized by using Box Behnken Design followed by a response surface methodology provided by Minitab®.

Results: The PCA grouped a range of gelling agents into three principal components (PC) based on the concentration, viscosity and spreadability. The results of PCA showed that Na CMC was the most suitable gelling agent for QUE nanoemulgel. To optimize the QUE nanoemulgel formulation, sixteen runs of BBD were successfully fabricated, providing an optimum-validated composition of 21.45 g, 13.96 g, and 4.00 g for Kolliphor® RH 40, Transcutol®, and Na CMC, respectively, with composite desirability of 0.843.

Conclusion: We successfully conducted gelling agent profiling by providing three types of PC using PCA. An optimized and validated formulation of QUE nanoemulgel was also successfully designed as a potential topical diabetic wound healing formulation.

Keywords: Quercetin, Nanoemulgel, Optimization, Principal component analysis, Response surface methodology

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INTRODUCTION

Foot diabetic wound is one of severe complications of the diabetic patients with uncontrolled blood sugar level, resulted in challenging recovery due to the risk of endothelial growth failure and angiogenesis blocking [1]. Tissue death and gangrene infection ended with amputation surgery of the extremity organs were the major risks and governed up to 50% of the diabetic wound cases [2, 3]. Enormous strategies have been done to promote foot diabetic wound recovery especially the use of phytochemical compounds [4]. Quercetin (2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one; QUE) is one of the natural compounds which is potential in promoting and recovering diabetic wounds [5, 6]. QUE shows antioxidant activity anti-inflammatory activity and promotes growth factors which are the key factors in regulating the wound healing process [7–9].

A nanoemulgel system is known as a result of the synergetic combination of nanoemulsion and the gelling system in a form of semisolid preparation [10–12]. Nanoemulsion shows excellent dissolving properties for lipophilic agents [13]. Nanoemulsion is also evidenced in maintaining the stability of the natural products in correlation with acidic pH conditioning [14]. The system of surfactant in the nanoemulsion formulation is essential in establishing a stable and good quality of the emulsion. In the previous study [15], we confirmed that an adequate combination of surfactant and cosurfactant supports the micellization of the nanoemulsion in solubilizing the lipophilic compound, showed by the high transparency of resveratrol nanoemulsion. The characteristic of such nanoemulsion has made the formulation [15] is of choice in delivering the QUE topically to the wound effectively. Nevertheless, low viscosity, thus uncontrolled spread-ability of nanoemulsion, may lead to the inconvenience of the application. However, incorporation of gelling agent enhances the viscosity. Various gelling agents have been widely used in the formulations of nanoemulgels ranged from natural and semi-synthetic polymers, such as tragacanth, xanthan gum, sodium alginate (Na alginate), carbomer, hydroxy-propyl methyl cellulose (HPMC) and sodium carboxymethyl cellulose (Na CMC). The difference of the structures, rheological properties, viscoelasticity nature, expanding mechanisms as well as the concentration of gelling agents in the system determines the gelling agents in affecting the consistency of the system [16–18].

Viscosity and the spread-ability are two of the important quality parameters in developing nanoemulgels, as they govern the physical consistency, physical stability and applicability of the preparation [11, 12]. Viscosity plays an important role in determining the rheological property during filling and packaging related to consistency-handling issues [19], whereas in an application, viscosity affects the ability of the product to spread over the intended topical area (spread-ability). The spread-ability leads to the ease of application thus the convenience of use.

Formulation by design (FbD) approach has addressed to develop such formulation in a rational, systematic and cost-effective manner [20]. Principle component analysis (PCA) can be applied as the first endeavor in profiling the prime components of formulation based on the expected physical performance prior to formula optimization [21]. Formula optimization using Box Behnken Design (BBD) in association with response surface methodology allows the formulators to build a rigid design of experiment with less risks of trial and error, thus enhancing the efficiency in formula design [15, 22]. Systematic formula optimization offers an excellent solution to establish the novel QUE nanoemulgels. This current study aimed to select a gelling agent with intended physical properties by the aid of PCA and to obtain the optimized composition of formulation to develop qualified QUE nanoemulgels.

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Original Article

THE EFFECT OF OLIVE OIL, TWEEN 60 AND SPAN 20 ON PHYSICAL CHARACTERISTICS OF QUERCETIN NANOEMULGEL

FETIANA CHRISMAURIN[1], RINI DWIASTUTI[1], LUTFI CHABIB[2], HARTATI YULIANI[1]*

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ABSTRACT

Objective: This research aims to evaluate the effect of olive oil, tween 60, and span 20 on the physical properties of quercetin nanoemulgel.

Methods: In this research, quercetin was formulated into nanoemulgel using a variation of olive oil, tween 60, span 20, and sodium alginate as a gelling agent. The nanoemulgel physical properties (pH, viscosity, and spreadability), stability, and particle size were tested. The data were measured and evaluated using Minitab®18 software; if the p-value<0.05, it is stated that there is a statistically significant difference in the formula.

Results: The result showed that tween 60 has the greatest significant impact on pH, viscosity, and transmittance value with a p-value<0.05 for all, meanwhile span 20 has the greatest significant impact on the spreadability of the nanoemulgel preparations with a p-value<0.05 indicating that they are significantly different.

Conclusion: This study reported that the effect of olive oil, tween 60 and span 20, with different variations, significantly impacts the physical properties (pH, viscosity, and spreadability) of the nanoemulgel.

Keywords: Quercetin, Nanoemulgel, Olive oil, Tween 60, Span 20

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INTRODUCTION

Plants have been used for a long time to cure some diseases, including fungal or bacterial infections, and now some are used for standard treatments of several diseases. As a tropical country, Indonesia has a variety of plants that function as medicines. Many phytoconstituents and chemical compounds with different biological and pharmacological activities have been isolated and identified from medicinal plants [1–3]. Quercetin is a secondary metabolite that is classified as a flavonol. It is yellow in color, completely soluble in lipids and alcohol, insoluble in cold water, and sparingly soluble in hot water [1]. Quercetin has five hydroxyl groups whose presence determines their biological and pharmacological activity [4]. Besides, quercetin has many other pharmacological activities; some are antibacterial and antifungal activities that can be used to treat fungal and bacterial infections. Studies have shown that quercetin has broad-spectrum antibacterial activity; the antibacterial activities destroy the bacteria's cell wall and change cell permeability, affecting protein synthesis and expression, reducing enzyme activities, and inhibiting nucleic acid synthesis [5].

Lim *et al.* (2021) [6] studied that quercetin has antibacterial activity against *Propionibacterium acnes*-induced skin disorders by significantly trimming down the pro-inflammatory cytokine production in various *P. acnes*-stimulated cell lines by reducing the TLR-2 expression, matrix metalloproteinase-9 (MMP-9) mRNA levels, and phosphorylation of mitogen-activated protein kinase (MAPK). Other than that, Vipin *et al.* (2019) [7] stated that quercetin completely inhibited virulence factors, including biofilm formation, and showed a significant protective effect on HEK 293T cells infected with *P. aeruginosa* strains.

Quercetin has a solubility in water of less than 0.5 g/ml and solubility in organic solvents such as 2 mg/ml in ethanol. In addition, the penetration capacity of quercetin on the skin is minimal due to its insoluble in water and lipophilic partition coefficient (logP = 1.82±0.32). A non-polar group in its structure and a polar hydroxyl group can also block quercetin's penetration into the skin [8]. Regardless of its many pharmacological effects on the skin, low hydrophilicity and poor percutaneous absorption are significant limitations to the conventional topical delivery of quercetin [9]. Due to its problem of penetrating the skin, numerous methods have been developed and investigated that increase the skin penetration capacity of quercetin. In this study, a nanotechnology approach was used. The nanotechnology-based drug delivery approach has heightened attention as a potential dosage form for topical delivery. The nanotechnology-based topical delivery of quercetin enhances the solubility and skin permeability increases the physicochemical stability, and provides sustain and control release profile. The type of formulation of nanotechnology-based topical delivery of quercetin is nanoemulgel preparations. The nanoemulgel formulation was chosen because it is suitable for delivering lipophilic drugs and difficult to dissolve in water [10–13]. Nanoemulgel can carry drugs using a low-energy solvent-free preparation method, and the efficiency of drug encapsulation is excellent compared to other lipid-based methods [14]. When the nanoemulgel contacts the skin, oil droplets will be released from the gel base. Then, the oil droplets will penetrate the stratum corneum directly, delivering drug molecules without going through the hydrophilic phase of the nanoemulsion [10].

The current study aimed to improve the delivery of topically applied quercetin due to its limitations by increasing its solubility and enhancing penetration into the buccal cavity through a nanoemulgel-based delivery system. A nanoemulgel loaded with quercetin was incorporated into a hydrogel system to enhance penetration.

MATERIALS AND METHODS

Materials

Quercetin(Merck®), virgin olive oil (Filippo Berio®), sodium alginate, tween 60, span 20, aquadest. The used instruments are UV-Vis spectrophotometer single beam (Shimadzu UVmini-1240), hotplate and magnetic stirrer (Thermo Scientific), Brookfield viscometer (Brookfield LVDVE 8673144), *particle size analyzer* (PSA) (HORIBA Scientific SZ-100), *centrifuge*, eppendorf tube, ultrasonication (Branson 3800) and pH meter.

Nanoemulsion and nanoemulgel preparation

The nanoemulsion preparation is an early stage before the finished preparations, which is nanoemulgel. The olive oil was put into a

beaker glass along with tween 60, span 20, and quercetin. The mixture was stirred using a magnetic stirrer for 20 min at 1000 rpm. After 20 min, aquadest was added at a temperature of 70°C little by little using a pipette, and the stirring speed was increased to 1250 rpm. Sonication was carried out for 50 min to remove bubbles. The test of the nanoemulsion type was carried out using the dilution method. The test was carried out by dissolving the sample into the water phase (1:100) and the oil phase (1:100) [15]. Based on the procedure reported by Mulia *et al.* (2018) [16], with slight modification, the preparation of nanoemulgel is carried out after the stable nanoemulsion preparation is finished. The quercetin-loaded nanoemulsion is fabricated into the nanoemulgel using sodium alginate, the gel base, then the preparation needs to stirring, and allowed to stand for 24 h.

Table 1: Formula of quercetin nanoemulsion

Materials	Use
Quercetin	Active ingredients
Ethanol 70%	Solvent
Tween 60	Surfactant
Span 20	Co-surfactant
Olive oil	Oil phase
Aquadest	Water phase
Sodium alginate	Gelling agent

Organoleptic

All the samples of nanoemulgel were physically observed every week for four weeks. Parameters observed included color, odor, and visually visible phase separation [16].

pH analysis

The pH of the nanoemulsion and nanoemulgel preparation was measured using a pH meter that had been calibrated using a standard solution at pH 4 or 7. The pH measurement was carried out in three replicates at room temperature [15, 16].

Viscosity

Measurement of the viscosity of the preparation was carried out using a Brookfield viscometer (Brookfield LVDVE 8673144) using 500 ml of the nanoemulgel preparation being put into a beaker glass and then selecting the appropriate spindle number. Measurements were carried out on day 1, day 3, and day 6.

Spreadability

The spreadability test of nanoemulgel was carried out by applying pressure to 0.5 g of the sample, which was placed on a flat acrylic of standard dimensions (20x20 cm) with a weight of 150 g. Each preparation's distribution area (diameters) was observed and measured [17, 18].

Measurement of transmittance value

The transmittance measurement was carried out using a UV-Vis spectrophotometer with a wavelength of 650 nm and keeping the aquadest (distilled water) as blank. Samples were made in a concentration of 1 mg/ml. The transmittance value is close to 100%. It can be considered that the samples have a nano size [19].

Particle size measurement

The particle size of the nanoemulsion preparation was measured using the dynamic light scattering (DLS) method with a particle size analyzer (PSA) using 10 ml of the samples dissolved with aquadest in a ratio of 1:1 [14, 19].

Accelerated stability testing

The measurement of the stability of the preparation was carried out with two tests. The first one is done by centrifugation test. The samples were put into an eppendorf tube and centrifuged for 5 min at a speed of 5000 rpm. The stability of the samples was seen after centrifugation, whether phase separation was found or not [16]. The parameters of the stability of the samples were observed, including phase separation, precipitation, creaming, and cacking.

Furthermore, the freeze-thaw cycle test was carried out by storing the preparation at-15 ℃ for 48 h and then transferring it to 25 ℃ for 48 h. Parameters measured for stability were the pH of the samples and particle size using transmittance value. Freeze-thaw cycle test was repeated for three cycles [16].

Data analysis

The factorial design was used as a statistical optimization of the formula in this study. The factorial design chosen is two levels and three factors. Then a three-way ANOVA test was carried out using Minitab® 18. If the p-value<0.05, it is stated that there is a statistically significant difference [20].

Table 2: Design factorial formulations scheme

Formula	Olive oil (g)	Tween 60 (g)	Span 20 (g)	Quercetin (g)
(1)	2	7	2	0.2
a	3	7	2	0.2
b	2	9	2	0.2
ab	3	9	2	0.2
c	2	7	3	0.2
ac	3	7	3	0.2
bc	2	9	3	0.2
abc	3	9	3	0.2

RESULTS AND DISCUSSION

Formulation consideration

The selection of each material and excipient used in the formula should be considered to ensure the safety and effectiveness of the nanoemulgel preparations. In this study, ethanol 70% was used as a solvent to dissolve quercetin because quercetin is insoluble in water and soluble in nonpolar solvents such as ethanol. The significant components in nanoemulgel are oil, surfactant, and cosurfactant. Oil is one of the critical components because oil also acts as a penetration enhancer [21]. In this study, olive oil is used as an oil phase in nanoemulsion preparations because it has an effect as an emollient to treat skin inflammation and soften skin with eczema or atopic dermatitis [34]. Olive oil is a fixed oil derived from the fruit *Olea europaea*. Olive oil is clear, colorless, or greenish-yellow in color and is an oily liquid. Olive oil is soluble in ethanol 95%, miscible with ether, chloroform, petroleum, and carbon disulfide. Olive oil is widely used in topical pharmaceutical formulations because it is a non-irritant and non-toxic compound. Olive oil has monounsaturated and polyunsaturated fatty acids, therefore making olive oil chemically and physically stable [22]. Tween 60 was used as a surfactant, and span 20 was used as a cosurfactants in this formula. Surfactant and cosurfactant work together to decrease the interfacial tension between two immiscible liquids to the transient negative value. Fine droplets are formed at this negative value due to the interphase expansion. Many surfactants or cosurfactants get absorbed on the surface until the bulk condition is source enough to make the interfacial tension positive again [21]. Tween 60 and span 20 are nonionic surfactants with less irritating effects on the human skin and the capability to form different nanocarriers easily [23].

Besides, nonionic surfactants have a safer toxicology profile, generally accepted orally [24]. Sodium alginate was used as a gelling agent to make the nanoemulgel preparations. Sodium alginate is an anionic hydrophilic heteropolysaccharide. Sodium alginate is widely used in the pharmaceutical industry due to its rheological properties because it can retain water and gel-forming, viscosity, and stabilizing properties. Besides, alginate-based particles are used for drug delivery due to their inherent properties, such as good biocompatibility and biodegradability [25].

Physical properties and stability tests of quercetin nanoemulgel

Organoleptic

The physical appearance of a nanoemulsion and nanoemulgel preparation is an essential factor need to be considered. The physical appearance (organoleptic) is related to the acceptance of the preparation to the patient. The physical appearance of nanoemulsion preparation was obtained with a liquid consistency, clear and slightly yellowish in color. Meanwhile, for nanoemulgel preparation, the texture is quite thick, like a gel in general, slightly yellowish, with an odor comparable the olive oil, which was acceptable. The type of nanoemulsion was oil in water (o/w) which nanoemulsion is formed when the surfactant is solubilized in the water phase [21]. The o/w nanoemulsion proclivity to solubilize hydrophobic and hydrophilic active components in their structure improves the delivery of active components or drugs [26].

Transmittance value

The particle size was measured twice using a UV-Vis spectrophotometer and a particle size analyzer (PSA). The UV-Vis spectrophotometer measures the transmittance value at the wavelength of 650 nm. The maximum transmittance value (or close to 100%) indicates the clarity of a particular mixture or transparent dispersion of nanoemulsion; the smaller particle size would be [19, 27]. The transmittance value ranges for the eight formulas are shown in table 3. Based on the measurement, the highest transmittance value came from formula b, formula ab, and formula (1), obtained at 99.83%±0.115, 96.30%±0.519, and 95.37%±0.231, respectively. This number shows that the result of the three formulas has clearer dispersion than other formulas. Nanoemulsion can get a high transmittance value because it doesn't disperse light on visible wavelengths [19]. However, a high transmittance value is insufficient to prove that the formula has formed the nanoemulsion. Thus, some characteristics, such as particle size measurement, are performed.

pH measurement

pH is a diagnostic biomarker and plays an essential role in preventing periodontal disease. Saliva is a dilute fluid made up of over 99% of water. Saliva has a normal pH range of 6.2–7.6, with 6.7 being the average pH. In the oral cavity, saliva maintains the pH near neutrality (6.7–7.3) [28]. The buccal cavity pH decreases to acidic conditions when inflammation or several diseases occurs. The pH range measured was still within the acceptable pH range (4.5-6.5) [16].

Viscosity and spreadability tests

The other essential factors are the viscosity and spreadability of the nanoemulgel preparations. These two factors affect the retention time of the trial and application to the skin area, which will impact the therapy's effectiveness [29]. The viscosity measurement was done on day one, three, and six after nanoemulgel preparation. Viscosity is the rheological parameter concerned with the physical and mechanical properties of the nanoemulgel, such as hardness, spreadability, and consistency [30]. The viscosity of each formulation was tested using a Brookfield viscometer with spindle number 62 at a speed of 12 rpm [31]. The viscosity results range from 2487–2499 cps. As shown in table 3, the formula 1, ab, and bc have a greater viscosity than other formulas, which are 2499±0, 2499±0, and 2499±0.155, respectively. But there is no difference in viscosity on day one, three, and six because the concentration of sodium alginate was the same in all formulations. So that was considered that all of the formulations are quite stable. This study found that the formulated nanoemulgel has a soft and smooth texture that is easy to apply. The spreadability ranges from 5.0–5.4 cm, indicating that all the formulations had good results and were easily spreadable.

Table 3: Results of physical properties of quercetin nanoemulsion and nanoemulgel

Formula	*pH nanoemulsion	*pH nanoemulgel	*Viscosity (cps)	*Spreadability (cm)	*Transmittance value (%)
(1)	5.20±0	5.63±0.153	2499±0	5.0±0.082	95.37±0.231
a	5.17±0.153	5.60±0.100	2494±1.732	5.1±0.126	91.77±0.058
b	4.90±0.100	5.63±0.053	2494±0	5.3±0.238	99.83±0.115
ab	4.80±0.100	5.53±0.058	2499±0	5.0±0.126	96.30±0.519
c	5.33±0.115	5.63±0.580	2487±0	5.2±0.082	89.70±0
ac	5.40±0	5.60±0.100	2494±0	5.2±0.163	92.87±0.115
bc	5.10±0.100	5.53±0.058	2499±0.155	5.1±0.050	91.53±0.551
abc	5.10±0	5.57±0.058	2497±0	5.4±0.096	95.27±0.153

*mean±SD, n=3

Accelerated stability testing

All eight formulations were subjected to freeze-thaw cycle testing where the samples were subjected to two extreme temperatures, which in this study are-15 ℃ and 25 ℃, and centrifugation. There was no sign of phase separations for any formulations after the centrifugation, indicating that the nanoemulgel would be stable even under such conditions. Therefore, after the freeze-thaw cycle, the parameters were evaluated using a UV-Vis spectrophotometer and pH meter with a similar procedure described previously. The results are shown in table 4. It is shown in table 4 that the transmittance value significantly decreased except for formulas b and ab; other than that, the transmittance value indicates that the preparations are not in nanoparticle form. The pH of each formulation was also measured at the end of the cycle and showed an increase, as shown in table 4. This is due to the reason that the oil phase and water phase would be generated at the end of the freezing process, and the unfrozen solutes will increase with the number of cycles so that it could shift the pH of the formulation [16] Besides, there is a phase separation and precipitation after the freeze-thaw cycle.

Table 4: Results of accelerated stability tests

Formula	pH	*Transmittance value (%)
(1)	5.0	48.87±1.563
a	5.0	71.63±0.321
b	5.0	94.23±0.723
ab	4.8	92.93±0.115
c	5.0	13.43±0.058
ac	5.0	12.27±0.115
bc	5.1	13.93±0.058
abc	5.1	53.07±0.153

*mean±SD, n=3

Particle size measurement

The particle size of the preparations was measured using a particle size analyzer (PSA) with the dynamic light scattering (DLS) method. The eight formulations and the one formula with the highest transmittance value (formula b) were measured in triplicate. As shown in fig. 1–fig. 3, the obtained size of the one formula with the highest transmittance value is 25.1, 28.1, and 31.7 nm (28.3±3.305), the measure was acceptable to be considered a nanoparticle because it was within 20–500 nm [32]. Meanwhile as shown in fig. 1–fig. 3, the polydispersity index (PDI) value obtained 0.418, 0.391, and 0.394 (0.401±0.015). The PDI values were considerably low, indicating good monodispersity and good stability. The PDI value reflects the distribution and uniformity of the oil droplets. PDI value for oral nanoemulsion formulation is less than 0.5, indicating the uniformity of droplet size distribution and affirming their homogeneity, as previously reported [33]. As shown in table 5, the eight formulations were categorized as nanoemulsions because the average droplet size and PDI value were accepted within the range. Furthermore, based on particle size and PDI value, formula b was selected as an optimized formulation for further studies.

Table 5: Results of particle size measurement

Formula	*Average droplet size (nm)	*PDI
(1)	20.20±0.458	0.304±0.024
a	296.00±2.254	0.414±0.069
b	18.33±0.058	0.364±0.009
ab	27.97±0.586	0.366±0.022
c	100.43±0.058	0.413±0.042
ac	42.63±0.153	0.374±0.006
bc	103.17±0.503	0.431±0.055
abc	62.43±0.451	0.184±0.061

*mean±SD, n=3; PDI-Polydispersity index

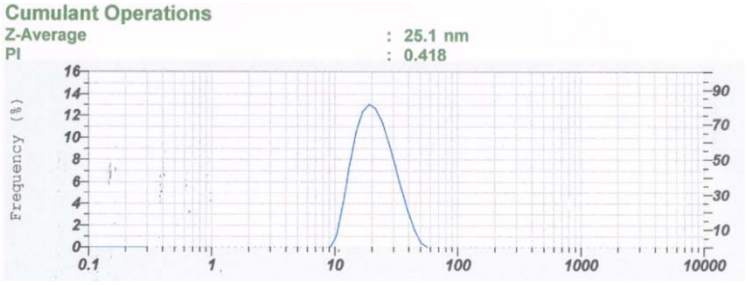

Fig. 1: Particle size and polydispersity index of formula b (first replication)

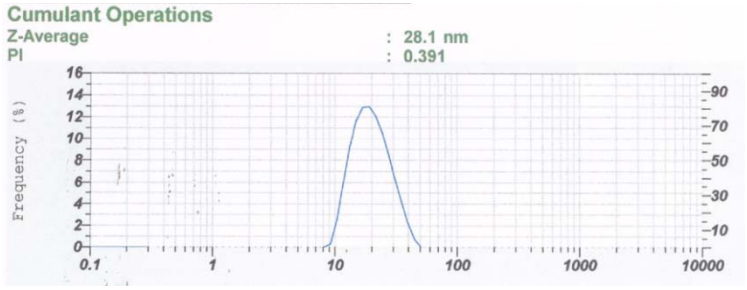

Fig. 2: Particle size and polydispersity index of formula b (second replication)

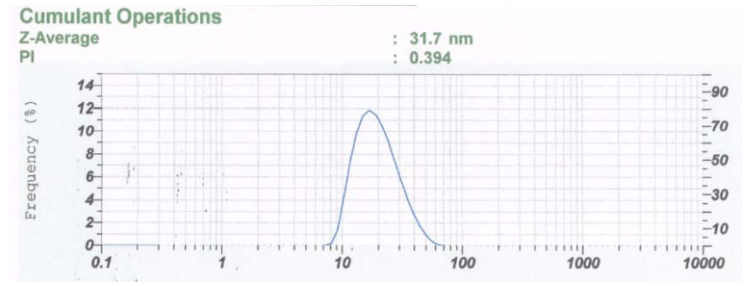

Fig. 3: Particle size and polydispersity index of formula b (third replication)

Data analysis

The data analysis was analyzed using Minitab®18. Data analysis was carried out on the pH measurement, viscosity measurement, spreadability test, and measurement of transmittance value to confirm the effect of olive oil, tween 60, and span 20 on the formula. From the ANOVA data analysis, the pH has the significant model because the p-value is<0.05 (0.000), indicating that olive oil, tween 60, and span 20 significantly affect the formula. The most incredible impact for the formula came from tween 60 with the f-value of 64.80

and p-value<0.05, which indicates that tween 60 has a significant effect on the pH of nanoemulgel preparations.

The viscosity of the formula also has a significant model because the p-value is<0.05 (0.000), indicating that olive oil, tween 60, and span 20 have a significant effect on the formula. Tween 60 has a significant impact on the viscosity of nanoemulgel with an f-value of 162.77 and p-value<0.05 (0.000), which indicates that tween 60 has a significant impact on the viscosity of nanoemulgel preparations.

The spreadability of the formula also has a significant model because the p-value is<0.05 (0.001), indicating that olive oil, tween 60, and span 20 have a significant effect on the formula. The spreadability was impacted by span 20 with the f-value of 19.36 and p-value<0.05 (0.000), which indicates that span 20 significantly affects the spreadability of nanoemulgel preparations.

The transmittance value of the formula also has a significant model because the p-value is<0.05 (0.000), indicating that olive oil, tween 60, and span 20 have a significant effect on the formula. The transmittance value was impacted by tween 60 with the f-value of 649.70 and p-value<0.05 (0.000), which indicates that span 20 significantly affects the spreadability of nanoemulgel preparations.

Table 6: Statistical analysis of physical properties

Formula	pH		Viscosity (cps)		Spreadability (cm)		Transmittance value (%)	
	[a]F value	[b]P value	[a]F value	[b]P value	[a]F value	[b]P value	[a]F value	[b]P value
Model	14.60	0.000	96.18	0.000	5.94	0.002	296.24	0.000
Olive oil	0.20	0.661	52.00	0.000	0.64	0.435	0.31	0.584
Tween 60	64.80	0.000	162.77	0.000	0.00	1.000	649.70	0.000
Span 20	33.80	0.000	52.00	0.000	19.36	0.000	624.65	0.000
Olive oil*Tween 60	0.80	0.384	4.92	0.041	0.64	0.435	2.80	0.113
Olive oil*Span 20	1.80	0.198	30.77	0.000	7.84	0.013	707.85	0.000
Tween 60*Span 20	0.80	0.384	208.00	0.000	0.16	0.694	87.70	0.000
Olive oil*Tween 60*Span 20	0.00	1.000	162.77	0.000	12.96	0.002	0.65	0.432

[a]F value determined the variation has the significant impact, three-way ANOVA, [b]P value determined the significant values, three-way ANOVA

CONCLUSION

This study reported that the effect of olive oil, tween 60 and span 20, with different variations, significantly impacts the physical properties (pH, viscosity, spreadability, and transmittance value) of the quercetin nanoemulgel. The result showed that tween 60 has the most significant impact on pH, viscosity, and transmittance value with a p-value<0.05 for all, meanwhile span 20 has the greatest significant impact on the spreadability of the quercetin nanoemulgel preparations with a p-value<0.05, indicating that they are significantly different.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally to this research article.

CONFLICT OF INTERESTS

The authors declared that no conflict of interest should arise concerning the authorship of this research article.

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