International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Characterization of the *"Ultra Small Unilamellar Carrier System (USUC)"* Nanodispersion Optimal Formula from the Active Compound Quercetin

[1*]Ully Chairunisa, [2]Diah Kemala Sari, [3]Indra Makmur, [4]Rina Desni Yetti

[1,2,3,4] Pharmacy, College of Pharmacy (STIFARM) Padang, Indonesia

*Email: ullychairunisa1234@gmail.com

DOI: https://doi.org/10.55248/gengpi.2022.3.10.28

ABSTRACT

Quercetin is a flavonoid compound with strong antioxidant activity found in various plants. The permeability of quercetin into the skin is very low due to its poor water solubility which makes its transdermal delivery inefficient. As a drug delivery system, USUC can increase the effectiveness of drug therapy by reducing the particle size to the nanometer range. The results of the evaluation of the nanodispersion preparation base obtained were stable in the form of a clear, yellow, distinctive aroma resulting from the addition of lecithin and homogeneous, the average pH was 6.8, the turbidity measurement was 0.050%, *freeze and thaw testing*, namely the stable preparation was stored at room temperature. as well as extreme temperatures, 52 cp viscosity and 1.073 g/ml specific gravity. The results of the evaluation of the quercetin nanodispersion preparation obtained were stable in the form of a clear solution, yellow in color, characteristically flavored resulting from the addition of lecithin and homogeneous, the average pH was 6.4, the transmittance measurement was 94.519%, *freeze and thaw testing*, namely the stable preparation was stored at room temperature. as well as extreme temperatures, viscosity 52 cp, specific gravity 1.062 g/ml, irritation test which was negative for all parameters observed, the maximum wavelength of quercetin was 371.50, the regression equation for quercetin was linear and the encapsulation efficiency value obtained was 96.22%. The results of characterization using PSA obtained a particle size of 11.0 nm , polydispersity index 0.243, and a zeta potential value of -11.4 mV.

Keywords: Quercetin, Nanodispersion, *USUC.*

INTRODUCTION

Quercetin is a flavonoid compound with strong antioxidant activity found in various plants including apples, *berries*, *brassica* vegetables ,*capers* , grapes, onions, leeks, tea, tomatoes, as well as in many grains, nuts, flowers, bark. , and leaves. Quercetin is also contained in medicinal plants including *ginkgo biloba, Hypericum perforatum*and *elderberry* .(Yang *et al.,* 2020) . Besides having strong antioxidant activity, quercetin can also protect keratinocytes from exogenous oxidizing agents and free radicals, prevent depletion of endogenous antioxidants and inhibit lipid peroxidation due to UV exposure (Hatahet*et al.,* 2016) . Despite these promising properties, the permeability of quercetin to the skin is very low due to its poor solubility (Castangia*et al.,* 2013) , the solubility of quercetin in water is only about 0.01 mg/ml (25˚C) (Wang *et al.* ., 2016) makes its transdermal delivery inefficient. Various formulation approaches are taken to increase its dermal penetration (Hatahet*et al.,* 2016) .

"Ultra SmallUnilamellar Carrier System (USUC)" is a vesicle delivery system that has an ultra small particle size of 0-40 nm which is also called a *"nanotop"*. USUC has a membrane consisting of phospholipids and cosurfactants. Lecithin is used in preparations as a phospholipid with tween 80 as a cosurfactant. As a drug delivery system, USUC can increase the effectiveness of drug therapy. By reducing the particle size to the nanometer range, the solubility of the drug can be greatly increased so as to increase bioavailability and therapeutic efficacy by maximizing drug penetration into the lowest layers of the skin, also minimizing side effects and toxic reactions (Tadros, 2015; Muliа*et al.,* 2018). . Nano-sized carriers can easily penetrate skin pores with small droplets and reach the target system, resulting in effective drug delivery (Tahara*et al* ., 2012) .

RESEARCH METHODS

Tools and Materials

The tools used in this study included: 100 ml infusion bottle, erlemeyer, analytical balance (Shimadzu®, Japan), burette, beaker glass, thermometer, watch glass, metal spatula , dropper, object glass, coverglass, viscometer (*Brookfield DV2T* , Japan), pH meter ATC (Volteraft®, Germany), volume pipette, *UV-Vis Spectrophotometry*, PSA *(Particle Size Analyzer)* and Zeta potential and "HORIBA" .

The materials used in this study include: quercetin (Sigma Aldrich) , aquadest (Novalindo), *Virgin Coconut Oil* (VCO) (Shakar Soya Products), Les itin (Sakar Soya Products) and Tween 80 (Barataco).

WORK PROCEDURES

Quercetin Raw Material Inspection

Quercetin examination was carried out according to the methods listed in *The Merck Index* including: Organoleptic, solubility and identification (The Merck Index, 1983).

Nanodispersion Formula

NO	FACTOR	CONCENTRATION
1	80 tween concentration	28.5%
2	Lecithin Concentration	1%
3	VCO concentration	2.5%
4	Mixing time	15 minutes
5	Stirring speed (rpm)	2000 rpm

Table 1. Nanodispersion base formula

Preparation of Nanodispersion Preparation Base Formulation

The working procedure was started by mixing tween 80 with lecithin then stirred with *Thinky Mixer* for 15 minutes at 2000 rpm, then added the oil phase (VCO) and stirred again using *Thinky Mixer* for 15 minutes at 2000 rpm to form a mixture of surfactant and oil. After that, add aquadest little by little above *the Thinky Mixer* until the volume of the preparation is 100 ml then stir again using *a Thinky Mixer* for 15 minutes at 2000 rpm (Damayanti*et al.,* 2019).

Evaluation of the Nanodispersion Preparation Base

1. **Organoleptic Examination**

This examination was carried out to see the physical appearance of the nanodispersion formulaincludes observations of color, odor, shape and homogeneity of the preparation (Damayanti*et al.,* 2019).

2. **pH check**

The pH measurement was carried out using a calibrated pH-meter. Measurements were carried out at room temperature. The pH of the preparation must be at pH 5-7 which is the pH of the skin (Damayanti*et al.,* 2019).

3. **Turbidity Calculation**

Turbidity was determined by measuring the turbidity of the base using UV-Vis spectrophotometry at 502 nm. The results obtained are then calculated using the equation to determine the percent turbidity.

4. **Freeze *and thaw***

To see changes in the stability of the nanodispersion preparation base. The preparations were stored at 25ºC for 24 hours and -5ºC for 24 hours. This cycle was repeated three times and the changes were recorded (Kale &Deore, 2016) .

5. **Viscosity testing**

Viscosity measurements were carried out with a *Brookfield Viscometer* , using spindle number 3 with a speed of 100 rpm. The results obtained are then recorded and repeated three times (Damayanti*et al.,* 2019).

6. **Specific Gravity**

Specific gravity was determined using a 10 ml pycnometer by cleaning the pycnometer by rinsing with distilled water, then dried. Then the empty pycnometer was weighed (w_0). Then the pycnometer was filled with aquadest, weighed and recorded the result (w_1). Dry again and then the pycnometer filled with the nanodispersion preparation was weighed and recorded the results (w2). Do three repetitions (Martin &Camarata, 2008).

Preparation of NanodispersionPreparationsQuercetin

Weighed 3 mg of quercetin, then dissolved in the oil phase (VCO), lecithin and tween 80 were stirred using a *Thinky Mixer* at 2000 rpm for 15 minutes. Mix the oil phase which already contains quercetin, then in the mixer again at 2000 rpm for 15 minutes. Then add distilled water little by little until the volume of the preparation is 100 ml at a speed of 2000 rpm for 15 minutes (Damayanti*et al.*, 2019).

Evaluation of NanodispersionPreparationsQuercetin

1. **Organoleptic Examination**

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3. **Calculation of % Transmittan**

The transmittance calculation was carried out using UV-Vis Spectrophotometry at a wavelength of 650 nm. The transmittance value close to 100% indicates a nanodispersion-sized mixture (Makula*et al*., 2017) .

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7. **Skin Irritation Test**

The irritation test was carried out by a closed patch test on human skin *(path test)* . The trick is that the nanodispersion preparation is taken about 0.2 ml then applied to the neck below the ear and then covered with *a waterproof hansaplast*and then observed the reaction that occurs. Observations were made for 24 hours. Observed symptoms such as redness, swelling and itching of the skin. This irritation test was carried out on 10 volunteers who had met the inclusion criteria including: physically and mentally healthy, aged 20-35 years, had no previous history of skin allergies and were not sick (fever) when the test took place (Robiyanto&Untari, 2018). .

8. **Determination of Quercetin Wavelength**

Weighed 10 mg of quercetin dissolved in 80% ethanol in a 100 ml (100 ppm) volumetric flask. Pipette as much as 5 ml of 100 ppm quercetin mother liquor, complete with 80% ethanol to 10 ml (50 ppm). Then 0.5 ml of 50 ppm mother liquor was pipetted into a test tube and added 1.5 ml of Pa ethanol, 0.1 ml of 10% $ALCL_3$, 0.1 ml of 1 M sodium acetate and 2.8 ml of distilled water, respectively. into the test tube. Determine the maximum wavelength of quercetin using UV-Vis spectrophotometry in the wavelength range of 400-800 nm.

9. **Preparation of the Quercetin Standard Solution Calibration Curve**

Make a series of solutions with concentrations of 30 ppm, 40 ppm, 50 ppm, 60 ppm, 70 ppm by pipetting 3, 4, 5, 6 and 7 ml of a 100 ppm concentration solution into a 10 ml volumetric flask and fill with 80 ethanol. % to the limit mark. 0.5 ml of each concentration was pipetted, put into a test tube and added 1.5 ml of ethanol Pa, 0.1 ml of 10% $ALCL_3$, 0.1 ml of 1 M sodium acetate and 2.8 ml of distilled water, respectively. come along. Calculate the absorption at the maximum wavelength. After that, make a curve of the relationship between concentration and absorption, so that a curve called a calibration curve is obtained and calculate the regression equation.

10. **Determination of Encapsulation Efficiency (% EE) of Quercetin Nanodispersion Preparations**

Determination of Encapsulation Efficient (EE) is used to determine the amount of drug present in the formulation. The weighed amount of the formulation is dispersed in an organic solvent by ultrasonication. In this study, 4 ml of the nanodispersion preparation was dissolved in 8 ml of 96% ethanol and then sonicated for 10 minutes. Then vortex until completely mixed. Then centrifuged for 30 minutes to form 2 layers. The clear layer was taken and the absorbance calculated at the maximum wavelength by UV-Vis spectrophotometry.

Characterization of NanodispersionPreparationsQuercetin

The examination of globule size, zeta potential and polydispersity index (PP) was carried out using a *Particle Size Analyzer* (PSA). The required amount of formulation is dispersed in double distilled water to obtain a homogeneous dispersion and should be used immediately (Gurpreet & Singh, 2018) .

RESULTS AND DISCUSSION

Inspection of raw materials for the active substance quercetin was carried out based on the requirements contained in *The Merck Index* (1983) .From organoleptic examination, quercetin is in the form of a crystalline powder, pale yellow. Quercetin is practically insoluble in water and readily soluble in ethanol. The results of the examination of the active substance have met the requirements contained in the literature. After examining the raw materials , the nanodispersion base is made. After making the base, then an evaluation is carried out to determine the stability of a base within a certain storage period. Evaluation of the base of this nanodispersion includes observation of organoleptic, pH, turbidity, *freeze and thaw test* , viscosity and specific gravity. Organoleptically, the base observed for 4 consecutive weeks remained stable in the form of a clear solution, yellow in color, characteristically flavored resulting from the addition of lecithin and homogeneous, there were no organoleptic changes.

The pH test carried out on the basis of the nanodispersion preparation aims to determine the pH value of the preparation. In topical preparations, the pH value must be in the skin pH range, which is between 5-7 (wasitaatmaja, 1997). The suitability of the pH value will affect the skin's acceptance of the preparation. If the pH of the preparation is too acidic (less than 5) it can cause irritation to the skin, whereas if the pH of the preparation is too alkaline (greater than 7) it can cause a dry effect on the skin (Damayanti*et al.*, 2019) . The results of pH measurements on the basis of nanodispersion preparations carried out every week for 4 consecutive weeks showed that the preparation had a pH value that fell within the skin pH range of 6.8 . The base preparation has a pH value that is within the skin's pH range, so that when combined it will produce a pH that is safe for topical use.

Turbidity measurement shows the level of turbidity of the formed nanodispersion base. From the base formula whose absorbance has been measured using UV-Vis spectrophotometry, the average result is less than 1%, which is 0.050 %. Turbidity with a value below 1% indicates that the formed base has a clear appearance and small droplet size. *Freeze and thaw* testing was carried out to see the stability of the nanodispersion preparation base under the influence of various environmental factors such as temperature, humidity and light. From the results obtained, there was no difference before and after the *freeze and thaw test was carried out* on the basis of nanodispersion preparations. These results indicate that the nanodispersion base will remain stable when stored both at room temperature and extreme temperatures.

In the measurement of viscosity, the average result obtained is 52 Cp. When compared with the value of the viscosity of water, the viscosity of the base is greater than the viscosity of water, but when compared to the viscosity of the oil phase, namely tween 80, lecithin and VCO, the value of the base viscosity is much smaller because of the large mixture of the water phase compared to the oil phase so that the viscosity is small. These results indicate that the viscosity of the base of the nanodispersion preparation is affected by the ratio of the mixture of oil and water phases. It is known that the viscosity value for nanodispersion preparations ranges from 10-2000 Cp (Yulian*iet al.*, 2016) indicating that the nanodispersion dosage base has a viscosity value that has been included in the good viscosity range of nanodispersion preparations. The result of testing the specific gravity of the nanodispersion base after 3 repetitions was 1.073 gram/ml. The greater the specific gravity obtained, it means that the closer the arrangement of the particles in the nanodispersion preparation base so that a thicker preparation is produced.

The results of the organoleptic observations of the quercetin nanodispersion preparations produced for 8 consecutive weeks were the same as the organoleptic results obtained from the basic organoleptic observations, namely the preparations in the form of a clear, yellow, distinctive aroma resulting from the addition of lecithin and homogeneous. The results of organoleptic observations from week 0 to week 8 were stable, there were no organoleptic changes during storage even though it had been stored for 8 weeks. The result of measuring the pH of the quercetin nanodispersion preparation for 8 weeks was 6.4 , which when compared with the pH obtained from this base preparation was different. This could be due to the combination of the composition of the ingredients used and the pH of the active substance quercetin , which is 7.5 so that it can affect the pH of the quercetin nanodispersion preparation. However, the decrease in pH in the quercetin nanodispersion preparation is still within the skin pH range, so it is safe to use and does not cause irritation (Witono*et al.*, 2007). The results of measuring the pH of the quercetin nanodispersion preparation can be seen in Figure 1.

Figure 1. Results of pH Evaluation of Nanodispersion Preparations

The results of the percent transmittance test after 3 repetitions decreased. This can be caused by the reduced light intensity due to absorption by the solution through which UV-Vis light passes on the use of a spectrophotometer instrument. Even so, the average result of 3 repetitions of the percent transmittance obtained good results, which is 94,519%. Where if the percentage of transmittance of the quercetin nanodispersion preparation is close to the percent transmittance of aquadest which is 100%, then the nanodispersion preparation has a clarity or transparency similar to water (Thakkar *et al.*, 2011).

The results of the *freeze and thaw* test for the quercetin nanodispersion were the same as the results obtained from the *freeze and thaw test* on the basis, that is, there was no difference before and after the *freeze and thaw test* . These results indicate that quercetin nanodispersion preparations will also remain stable when stored at room temperature or extreme temperatures. The results of the *freeze and thaw* test observations can be seen in Figure 2. Likewisefor the viscosity test, the average results obtained from the quercetin nanodispersion preparation are also the same as the average obtained in the dosage base viscosity test, which is 52 Cp. The results of the observation of the viscosity test can be seen in Figure 3. Based on the results after 3 repetitions, the average density of the dosage base was 1.062 gram/ml. The results obtained from the specific gravity test are smaller than the results obtained from the test on the basis. The greater the specific gravity obtained, it means that the closer the arrangement of the particles in the nanodispersion preparation so that a more viscous preparation is produced.

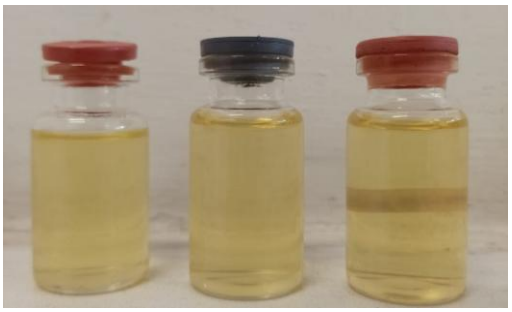
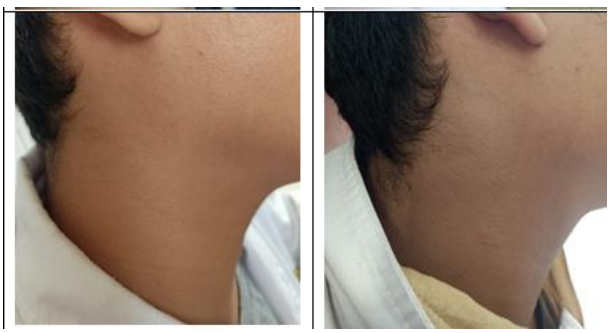
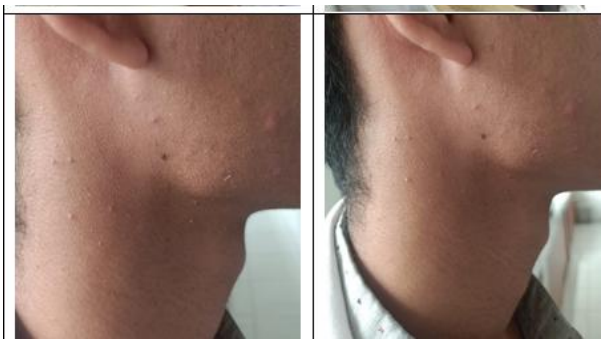


Figure 2 .*Freeze and Thaw* Test Evaluation Results for Nanodispersion Preparations

Figure 3 . Results of Evaluation of the Viscosity Test for Nanodispersive Preparations

The irritation test is carried out to see whether there is an effect of redness on the skin, swelling and itching of the skin. This test is carried out to ensure the preparation does not cause irritation to the skin in use for 24 hours. From the observation of skin irritation testing, quercetin nanodispersion gave negative results for all parameters observed, namely redness of the skin, swelling and itching of the skin. Based on the results of this test, it can be concluded that the preparation of quercetin nanodispersion does not cause an irritation reaction on the skin so it is safe to be used topically. The results of the irritation test evaluation can be seen in Figure 4.





(a) **(b)**

Figure 4 . Evaluation Results of the Irritation Test for Nanodispersion Preparations

(a) Prior to irritation test

(b) After the irritation test

Measurement of the maximum absorption wavelength in the standard solution of quercetin was carried out in the wavelength range of 400-800 nm. The maximum absorption wavelength of the quercetin standard solution obtained was 371.50 nm. The standard curve graph shows that the concentration is directly proportional to the absorbance value, the greater the concentration of the standard quercetin standard solution, the higher the absorbance value produced. The absorbance measurement obtained the quercetin regression equation y = 0.00363x + 0.24522 . The results of the linearity value are indicated by the correlation coefficient (r) of 0.99951 . The value (r) obtained is close to 1, indicating that the regression equation is linear. The results of the absorbance curve measurement can be seen in Figure 5.

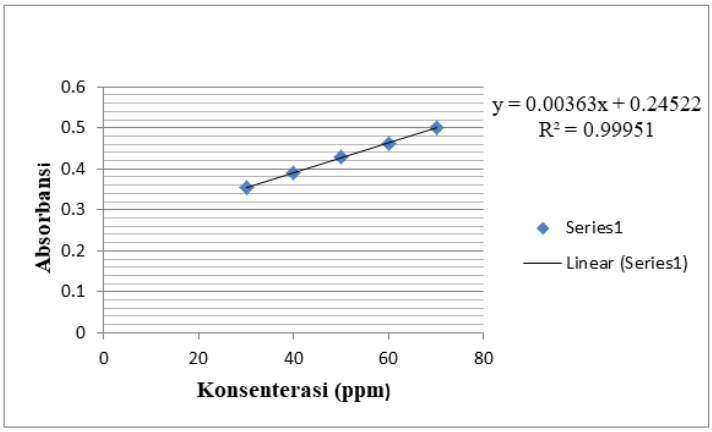


Figure 5. Graph of the quercetin calibration curve

The encapsulation efficiency (EE) of the quercetin nanodispersion preparation was determined by measuring the concentration of the drug adsorbed by the matrix system by centrifugation method. The average absorbance value obtained was used to calculate the percent efficient encapsulation of the quercetin nanodispersion preparation. The result of the efficient percentage of encapsulation obtained is 96.22 % . Where the percent efficient value of encapsulation is said to be good because it falls into the range of the targeted encapsulation efficiency value, which is 80-100% (Riliansa, 2021).

From the examination using PSA, the globule particle size was 11.0 nm , where this result fell into the desired nanodispersion size range of 0-40 nm. The results of the polydispersity index obtained are 0.243. The index polydispersity value is used to estimate the range of particle size distribution in a preparation and is used to determine whether there is aggregation or the gathering of particles into one to form large granules. Meanwhile, the zeta potential obtained is -11.4 mV , which means that this quercetin nanodispersion preparation is not stable enough for a long period of storage. The results of the examination using the PSA tool can be seen in Figure 2.

Formula	Particle size (nm)	Polydispersion index	Zeta potential (mV)
Quercetin nanodispersion	11.0	0.243	-11.4

CONCLUSIONS AND RECOMMENDATIONS

Conclusion

Based on the research that has been done, it can be concluded that the quercetin nanodispersion preparations are as follows:

1. Quercetin can be formulated into nanodispersion preparations " *Ultra Small Unilamellar Carrier System (USUC).*
2. Stability results which include organoleptic test, pH, transmittan, *freeze and thaw* , viscosity, specific gravity, irritation test, determination of wavelength, calibration curve and encapsulation efficiency (% EE) on quercetin nanodispersion preparations meet the specified requirements. For the results of characterization using PSA, the particle size obtained is 11.0 nm , polydispersity index 0.243, where these results are in accordance with the specified requirements. While the zeta potential value is -11.4 mV , which is less stable and not in accordance with the specified requirements.

Suggestion

It is recommended in further research to be able to conduct testing using TEM tools.

Reference

Castangia, I., Nácher, A., Caddeo, C., Valenti, D., Maria, A., Díez-sales, O., Ruiz-saurí, A., &Manconi, M. (2013). *Acta Biomaterialia Fabrication of quercetin and curcumin bionanovesicles for the prevention and rapid regeneration of full-thickness skin defects on mice .1* , 1–5.

Damayanti, H., Wikarsa, S., and Jafar, G. (2019). Nanoemulgel Formulation of Mangosteen Peel Extract *(Garcinia Mangostana L.), Indonesian Journal of Pharmaceutical Research,* 1(3), pp. 166-176, doi:10.33759/jrki.vli3.53

Gurpreet, K., & Singh, SK (2018). Review of nanoemulsion formulation and characterization techniques. *Indian Journal of Pharmaceutical Sciences ,80* (5), 781–789.

Hatahet, T., Morille, M., Hommoss, A., Devoisselle, JM, Müller, RH, &Bégu, S. (2016). Quercetin topical application, from conventional dosage forms to nanodosage forms. In *European Journal of Pharmaceutics and Biopharmaceutics* (Vol. 108, pp. 41–53). Elsevier BV

Kale, SN, &Deore, SL (2016). Solubility enhancement of Nebivolol by micro emulsion technique. *Journal of Young Pharmacists ,8* (4), 356–367.

Martin, A., &Camarata, A., (2008). *Physical Pharmacy Third Edition* . UI Press Publisher. Jakarta

Mulia, K., Putri, GA, &Krisanti, E. (2018). Encapsulation of mangosteen extract in virgin coconut oil based nanoemulsions: Preparation and characterization for topical formulation. *Materials Science Forum,* 929MSF (August), 234-242.

Riliansa, G, H, C., (2021). *Optimization of Soy Lecithin Concentration and Sonication Duration of Lipid Nanoparticle Formulation With 4-n-Butylresorcinol Active Ingredients Using Bath Sonicator: Factorial Design Application.* (Thesis). Yogakarta: Sanata Dharma University.

Tadros. (2015). *Nanodispersions.* De Gruyter.

Tahara, Y., Kaneko, T., Toita, R., Yoshiyama, C., Kitaoka, T., Niidome, T., Katayama, Y., Kamiya, N., &Goto, M. (2012). A novel double-coating carrier produced by solid-in-oil and solid-in-water nanodispersion technology for delivery of genes and proteins into cells. *Journal of Controlled Release ,161* (3), 713–721.

Thakkar, H., Nangesh, J., Parmar, M., Patel, D. (2011). Formulation and characterization of lipid-based drug delivery system of raloxifene-microemulsion and self-microemulsifying drug delivery system .*Journal of Pharmacy &Bioallied Sciences.* 3 (3). 442-449.

The Merck Index. (1983). *An Encyclopedia Of Chemical, Drug and Biological* (Tenth Edition). London: Harper and Row.

Wang, W., Sun, C., Mao, L., Ma, P., Liu, F., Yang, J., & Gao, Y. (2016). The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. *Trends in Food Science and Technology ,56* , 21–38.

Wasitaatmaja, S., (1997). *Medical Cosmetics Guide* . UI Press: Jakarta

Witono, Y., Aulanni'am, Subagio, A., &Wdjarnako, SB (2007). Characteristics of Hydrolyzed Soybean Protein Hydrolyzed Using Protease FromBiduri Plant (Calotropis gigantea). *Berk Penel .Hayati,* 13(03) ,7 -13.

Yang, D., Wang, T., Long, M., & Li, P. (2020). Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. *Oxidative Medicine and Cellular Longevity* , 23(4). 71-75.

Yuliani, SH, Hartini, M., Stephanie, Pudyastuti, B., &Istyastono, EP (2016). Comparison of Physical Stability Properties Of Pomegranate Seed Oil Nanoemulsion Dosage Forms With Long-Chain Triglyceride And Mediun-Chain Triglyceride As The Oil Phase. Traditional Medicine Journal, 21(2), 93-98.