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COMPARATIVE STUDY BETWEEN RESVERATROL NANOCREAM FORMULA AND CONVENTIONAL CREAM WITH DIMETHYLSULFOXIDE ADDITION

Dewi Fitriani Puspitasari*), Rahmawati Salsa Dinurrosifa

[1,2]STIFAR Yayasan Pharmasi Semarang, Jl. Letjend Sarwo Edie Wibowo Km.1, Semarang
**Email: fitrianidewi2019@gmail.com*

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INTISARI

Resveratrol memiliki aktivitas potensial sebagai antioksidan. Beberapa penelitian telah memformulasikan resveratrol ke dalam sediaan topikal, tetapi kelarutan resveratrol yang rendah menyebabkan pelepasan zat aktif yang rendah. Dimethylsulfoxide adalah bahan yang banyak digunakan dalam sediaan topikal, yang dapat digunakan untuk meningkatkan kelarutan zat yang sulit larut. Nanocream adalah penghantaran obat topikal berbasis nanopartikel. Ukuran globulnya berskala nano, yang dapat membantu meningkatkan kelarutan obat. Tujuan dari penelitian ini adalah untuk mengevaluasi karakteristik fisik dan uji disolusi antara sediaan krim yang diformulasikan dengan variasi konsentrasi DMSO dan sediaan krim yang diformulasikan ke dalam bentuk nano. Variasi penambahan konsentrasi DMSO pada sediaan krim konvensional resveratrol adalah 3%, 5% dan 7%. Metode penelitian diawali dengan memformulasikan sediaan krim nano resveratrol. Sediaan terdiri dari komponen lipid yang didispersikan ke dalam basis krim. Lipid yang digunakan terdiri dari VCO, tween 80 dan propilenglikol. Obat yang dimuat dalam lipid resveratrol sebanyak 300 mg, kemudian diuji nilai transmitansinya dan ukuran globulnya. Formula krim resveratrol konvensional dibuat menjadi FI, FII dan FIII, dimana masing-masing formula menggunakan konsentrasi DMSO yang berbeda. Analisis hasil uji disolusi diamati antara FI, FII dan FIII pada formula krim konvensional. Hasil uji disolusi dari ketiga formula tersebut juga dibandingkan dengan sediaan nanokrim resveratrol. Pengamatan hasil disolusi dinilai dari persentase zat aktif yang dilepaskan pada menit ke 5, 10, 15, 30, 45, 60. Hasil uji sifat fisik krim dengan penambahan DMSO menunjukkan tidak ada perbedaan pH dan hasil uji disolusi menunjukkan tidak ada perbedaan yang signifikan antar formula, sedang resveratrol nanokrim memiliki nilai disolusi yang lebih tinggi dibandingkan ketiga krim dengan penambahan DMSO.

Kata kunci: Uji disolusi, DMSO, nanocream, resveratrol.

ABSTRACT

Resveratrol has potential activity as an antioxidant. Several studies have formulated resveratrol into topical preparations, but the low solubility of resveratrol causes low release of the active substance. Dimethylsulfoxide is a widely used ingredient in topical preparations, which can be used to increase the solubility of poorly soluble substances. Nanocream is a nanoparticle-based topical drug delivery. The globule size is nanoscale, which can help improve drug solubility. The purpose of this study was to evaluate the physical characteristics and dissolution tests between cream preparations formulated with varying concentrations of DMSO and cream preparations formulated into nanoforms. The variation of DMSO concentration addition in resveratrol conventional cream preparation is 3%, 5% and 7%. The research method began with formulating resveratrol nanocream preparation. The preparation consisted of lipid components dispersed into a cream base. The lipids consisted of VCO, tween 80 and propylenglycol. Loading drug of resveratrol lipid was 300 mg, then tested for

transmittance value and globule size. Conventional resveratrol cream formula was made into FI, FII and FIII, where each formula used different concentration of DMSO. Analysis of dissolution test results was observed among FI, FII and FIII in conventional cream formulas. The dissolution test results of these three formulas were also compared with the resveratrol nanocream preparation. Observation of dissolution results was assessed from the percentage of active substance released at minutes 5, 10, 15, 30, 45, 60. The physical characteristics test results of creams with the addition of DMSO showed no difference in pH and the dissolution test results showed no significant difference. resveratrol nanocream has a higher dissolution value than the three creams with the addition of DMSO.

Key words: *Dissolution test, DMSO, nanocream, resveratrol*

Nama : Dewi Fitriani Puspitasari
Institusi : STIFAR Yayasan Pharmasi Semarang
Alamat institusi : Jl. Letnan Jendral Sarwo Edie Wibowo Km.1, Semarang
E-mail : *fitrianidewi2019@gmail.com*

INTRODUCTION

Resveratrol is a natural polyphenol with a stilbene group, found in blueberries, blackberries, nuts and grapes. Resveratrol is a polyphenolic compound that has potential activity as an antioxidant. Resveratrol is a strong inhibitor of NADPH and adenosine 5-diphosphate (ADP)-Fe+, inhibits the production of H_2O_2 and lipid peroxidase and prevents extracellular cell oxidative stress so that it can slow aging of the skin (Prerna, B. and Rita, 2014). Resveratrol is a compound that has a low solubility in water of 0,03 mg/L (Anita, V. H., and Sharad, 2017). An obstacle to topical drug administration is the presence of the outermost skin layer, the stratum corneum, which is the main barrier to drug penetration through the skin. Various techniques have been used in an attempt to overcome the efficient barrier function of the skin to facilitate drug delivery drug delivery through the stratum corneum.

Nanocream is a semi-solid preparation based on nanoparticles. Nanoparticles in nanocream preparations can help increase the solubility of active substances. Several studies formulated resveratrol into topical preparations, but the low solubility of resveratrol causes low release of the active substance. Resveratrol was formulated into a nanocream preparation, expected to increase the solubility of this active substance. The cream base of the nanocream preparation helps maintain stability in storage, easily washed off with water.

Dimethylsulfoxide is known as an enhancer of the solubility of active substances in preparations. Dimethylsulfoxide itself has dipolar aprotic properties, which means that the drug can dissolve both polar and non-polar compounds (Sum and De Pablo, 2003). The use of this component is expected to increase the solubility of resveratrol in the cream.

This research is intended to study the effect of increasing DMSO concentration on the physical characteristic and the dissolution test of conventional resveratrol cream and compared to resveratrol nanocream.

RESEARCH METHODS

The instruments used in the study were digital scales (Shimadzu®), Brookfield DV-1 Prime viscometer, *waterbath* (Memmet), vortex mixer (Thermolyne), pH meter (HANNA), paddle type dissolution test kit USP TDT-08L, spreadability test kit, UV spectrophotometer-1280 (Shimadzu), cellophane membrane (Spectrum®), PSA HORIBA SZ-100.

Materials: Resveratrol (Chromadex®), *virgin coconut oil* (Brataco®) with *foods grade*. Other ingredients were tween 80 (DOW®), propylenglycol (DOW®), stearic acid (Wilfarin®), TEA (Petronas®), cetyl alcohol (DOW®), methyl paraben (UENO®), propyl paraben (Clariant®), glycerin (DOW®), Dimethylsulfoxide (Merck®) with *pharmaceutical grade*. Potassium phosphate (Merck®), distilled water.

Formulation of resveratrol nanocream

The preparation of nanocream started with making resveratrol lipid. The nano cream preparation formula can be seen in Table I. VCO was used as oil component, surfactant combination of span 80 and tween 80, and propylenglycol as cosurfactant. The ratio of the three components was 1: 4 (25 and 75) : 8. Lipid loaded with 300 mg/mL resveratrol. One mililiters resveratrol lipid was added in the cream base (Eid *et al.*, 2014).

The cream base for the nanocream was prepared from the oil phase of cetyl alcohol, stearic acid and propyl paraben, which were put into a porcelain cup and then melted on a waterbath at 75°C. The water phase was made by mixing glycerin, TEA, methyl paraben and hot water. The oil phase that has melted completely is then mixed with the water phase, stirred to form a homogeneous cream base. The cooled cream base was then added with 300 mg of resveratrol dissolved lipid, then stirred until homogeneous.

Formulation of conventional resveratrol cream with DMSO

The preparation of the cream begins with melting the oil phase, then mixing it with the water phase, stirring until a base is formed. The cooled cream base was then added with dimethylsulfoxide and 300 mg of resveratrol, then stirred until homogeneous. Resveratrol cream formula with the addition of DMSO of various concentrations is shown in Table I.

Table I. Resveratrol Nanocream Formula and Conventional Cream with DMSO

Materials	Concentration (%w/w)			
	Nanocream	Cream with DMSO		
		FI	FII	FIII
Resveratrol	1	1	1	1
Lipid	3	-	-	-
DMSO	-	3	5	7
Stearic acid	2	2	2	2
Cetyl alcohol	7	7	7	7
Trietanolamin	0.5	0.5	0.5	0.5
Glycerin	15	15	15	15
Methyl paraben	0.2	0.2	0.2	0.2
Propyl paraben	0.1	0.1	0.1	0.1
Destilate water up to	100	100	100	100

Evaluation of the physical characteristics

Testing of preparations to determine the physical characteristics of nanocream preparations and resveratrol cream preparations with the addition of DMSO. Physical characteristics testing, including:

pH testing

pH testing is done using a pH meter.

Viscosity testing

The viscosity test was carried out using a Brookfield Viscosimeter. The sample is put into the tube until the calibration mark. Set the spindle and RPM pressed the start button observed the viscosity value (cps) on the Brookfield Viscosimeter screen.

Spreadability testing

The glass plate was equalized first then weighed 0.5 g of cream preparation and then applied to the center of the glass plate covered with mini block paper, allowed to stand for 5 minutes and then calculated the diameter vertically and horizontally. After that, the glass plate was given a load

of 50, 100, 150, 200, 250, 300 g respectively, allowed to stand for 5 minutes and then recalculate the diameter until constant results were obtained.

Organoleptical testing

This test is carried out by observing the physical characteristics of the cream preparation, namely color, and odor.

Globul size

Observations of globul size nanocream preparations were also made. The globule measurement of nanocream resveratrol was performed after diluted with water. Measurement using PSA Horiba.

Dissolution test of the preparation

This test is used to determine the release of active substances of drugs in vitro in the media. Tests were carried out using a paddle-type dissolution test kit and cellophane membrane and then measured using a visible spectrophotometer at a wavelength of 200-800 nm. The active substance release test in this study used phosphate-buffered media pH 7.4 and was set at 37°C conditioned like body temperature. Resveratrol nanocream and resveratrol conventional cream were tested for dissolution to compare the percentage of resveratrol release.

RESULT AND DISCUSSION

Resveratrol Nanocream Formulation

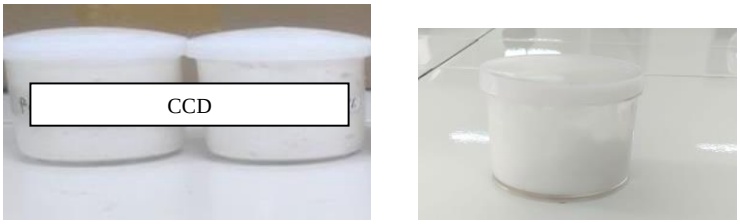
Virgin coconut oil in its solid state has a melting point of 24-27°C. Virgin coconut oil contains saturated fatty acids, including caprylic acid (5.54%), capric acid (5.01%), lauric acid which is very high (47.5%) and includes medium chain saturated fat (number of carbons 12) commonly referred to as Medium Chain Fatty Acid (MCFA). VCO also contains myristic acid (21.68%), palmitic acid (9.57%), stearic acid (1.85%) (EM *et al.*, 2023). Tween 80 is included in the nonionic surfactant group, the molecular weight is 1310 and the HLB of tween 80 is 15. The use of a combination of surfactants makes it possible to obtain a stable mixture and facilitate the adjustment of HLB needs.

Physical Characteristics Test Results

The results of the organoleptic test of the resveratrol nanocream and conventional cream with DMSO preparation showed that the preparation was white and homogeneous (figure 1). The results of the physical characteristics test of resveratrol nanocream and conventional cream with DMSO are shown in Table II. The pH test results show that the three formulas did not show significant differences in pH value. Increasing the DMSO concentration does not cause changes in the pH of the preparation. This is because DMSO has amphoteric properties, which act as a weak acid and weak base. The viscosity test results between resveratrol cream formulas (FI, FII, FIII) show that the viscosity decreases as the DMSO concentration increases. This decrease in viscosity is because DMSO has a liquid form, increasing the concentration of DMSO causes a change in viscositythis also correlates with the spreadability value of the three formulas. The viscosity and spreadability values between the three formulas showed significant differences ($p<0,05$). Spreadability describes the ability of the preparation to spread on the skin layer. The requirement for good spreadability is between 5-7 cm (Eliska *et al.*, 2016).

The results of the physical characteristics test of resveratrol nanocream, showed that the pH of the nanocream preparation was 6.24 ± 0.25, this is in accordance with the pH of topical preparations is 5-6 (Charoenkul and Phromyothin, 2017). Nanocream preparations are composed of resveratrol and lipid components, where the lipid component consists of tween 80, span 80 as a surfactant and propylenglycol as a cosurfactant. Resveratrol is an active component that has an acidic pH while tween 80 has a pH range of 6-8. the presence of lipid components has an effect on increasing the pH value of the preparation.Viscosity test results showed that nanocream had a higher viscosity of 15147 cps. Increased viscosity causes a decrease in the spreadability of the preparation. In order to determine the particle size of the nanocream preparation, readings were taken using PSA. particle measurement results showed that the nanocream had a size of 119.7 nm, and a polydispersity index

value of 0.455. The polydispersity index has a range of values from 0 to 1, a value close to 0 indicates a homogeneous dispersion, while a value greater than 0.5 indicates high heterogeneity (Kurniawan, 2012). The measurement results of resveratrol nanocream particles and polydispersity values are shown in Figure 2.



(a) (b)

Figure 1. (a)Result of Conventional Cream with DMSO (b) resveratrol nanocream

Table II. Physical Characteristics of Resveratrol Nanocream and Conventional Cream with DMSO (n=3)

Formula	pH	Viscosity	Spreadibilty	Organoleptic	Particle size
		(Cps)	(cm)		(nm)
Nanocream	6.24 ± 0.25[a]	15147 ± 40.1[a]	4.8 ± 0.1161[a]	White cream	119.7[a]
CCD FI	5.83 ± 0.147[#]	9255.8 ± 354.12*	5.78 ± 0.1161*	White cream	-
CCD FII	5.87 ± 0.149[#]	9669.2 ± 129.63*	6.10 ± 0.054*	White cream	-
CCD FIII	5.88 ± 0.153[#]	8902.6 ± 54.054*	6.64 ± 0.1104*	White cream	

CCD (Convencional cream with DMSO)
Data displayed with 3 times replication and standard deviation
[#]) not significant different between formulas (FI, FII, FIII)
*) significant different between formulas (FI, FII, FIII)
[a]) not compared

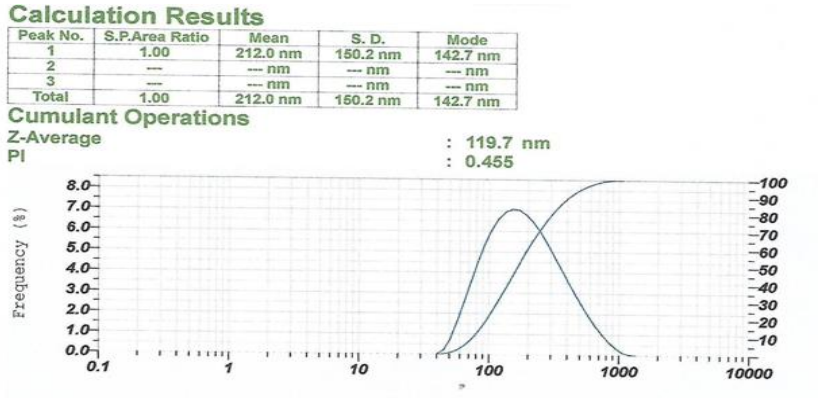


Figure 2. Measurement results of resveratrol nanocreams particles

Dissolution Test Results

The release of resveratrol from the base is influenced by the solubility of the drug, the partition coefficient of the drug, and the physico-chemical properties of the polymer. The solubility of the active ingredient also affects the release of the drug from the base (Sinko, 2011). Dissolution test

results of resveratrol cream formula with varying concentrations of DMSO and resveratrol nanocream, shown in Figure 3. It can be seen that in the 60th minute shows a release rate 1.19% ± 0.142 in FI, 2.05% ± 0.224 in FII and 1.75% ± 0.172 in FIII. Percent release of active substances between FI, FII, FIII did not show differences even though the DMSO concentration was increased. The dissolution test results of conventional resveratrol cream preparations showed that with increasing DMSO concentration, there was no significant difference in the concentration of active substances dissolved in the media. Dimethyl sulfoxide is a small amphiphilic molecule composed of a hydrophilic sulfoxide group and 2 hydrophobic groups. This amphiphilic nature is at the core of the interaction relationship between DMSO and the cell membrane. Studies show that DMSO accumulated in the head group region and weakened the lateral strength between ceramide molecules (the largest component of stratum corneum lipids) (Gironi *et al.*, 2020). Atomic-level simulations have shown that DMSO has 3 different effects on the cell membrane, depending on its concentration. At low concentrations (2.5-7.5 mol%), it induces expansion and thinning of the lipid bilayer, as described above, thus increasing the fluidity of the hydrophobic region of the membrane. At higher concentrations (10-25 mol%), DMSO induces the formation of temporary "water pores" in the cell membrane. In this study, DMSO was used in the low concentration range, where in this range DMSO induces expansion and thinning of the lipid bilayer, this thinning contributes to an increase in the dissolution value, but does not make a significant difference in the release of the active substance. Increasing the concentration of DMSO can be done, but at high concentrations, DMSO can have an irritating effect.

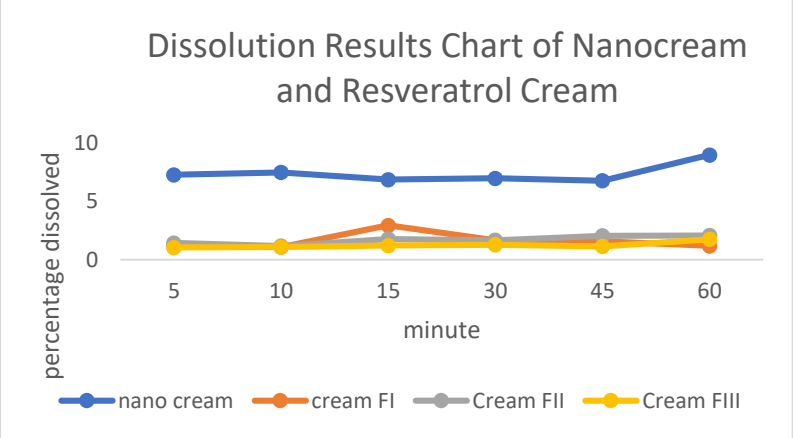


Figure 3. Comparison of dissolution test results of resveratrol nanocream preparation versus conventional cream

However, if the three formulas are compared to the nanocream preparation, it shows a significant difference between the formula and the nanocream preparation. Percent release of active substance in nanocream is higher than conventional cream preparation, although the viscosity value of nanocream preparation is higher than conventional cream. Percent release of active substances in nanocream 8.9%. Nanonisation is one of the successful methods in improving drug dissolution. The advantage of nanoparticle technology is that it can increase solubility. A study proved that nanoparticle modification can improve the results of dissolution tests on aceclofenac and capsicin compounds. Nanoemulsion, nanomicelle, nanomiemgel aclufenac and capsicin showed higher release of active substances compared to conventional gel preparations. The release test was performed using a USP type II device in 500 ml phosphate buffer pH 6.8, at 100 rpm and 37°C (Somagoni *et al.*, 2014). Similar results were found in the modification of fluconazole solid lipid nanoparticles. Solid lipid nanoparticles were able to enhance the dissolution of fluconazole in dissolution media (Moazeni *et al.*, 2016). An increase in the amount of release and permeation of BCS class II drugs was also shown in the modification of hydrocortisone nanoparticles (Hussain *et al.*, 2013). This mechanism occurs due to a reduction in particle size (e.g. to the nanometer range),

as a result of which the surface area of the particulate increases, resulting in an increased solubilization speed of the compound. This is aligned with Noyes Whitney equation (Ravichandran, 2013).

CONCLUSION

The results of the physical characteristics test of cream preparations with the addition of DMSO, showed no difference in pH value as the DMSO concentration increased, but there was a decrease in viscosity value as the DMSO concentration increased. The dissolution test results also increased with increasing DMSO concentration but were not significantly different. The physical characteristics of resveratrol nanocream showed that the pH value of the preparation met the skin pH range, had a nanometer-scale particle size, and the dissolution test results were significantly different from the three conventional cream formulas.

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