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Transfersomes for Optimal Penetration of α-Mangostin (*Garcinia mangostana L.*) in Cosmetic Products using Vortexing-Sonication

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ABSTRACT

Produk kosmetik berbasis transfersom semakin menarik perhatian karena teknologi nano vesikel ini dapat meningkatkan penetrasi bahan aktif seperti isolat manggis dari *Garcinia mangostana* L. ke dalam kulit. Teknologi ini menawarkan pengembangan produk kosmetik inovatif yang menjanjikan. Transfersom terdiri dari fosfolipid (yaitu fosfatidilkolin dari lesitin kedelai) dan surfaktan yang masing-masing membentuk vesikel dan meningkatkan fleksibilitas transferom sebagai aktivator tepi. Kami mengembangkan formula dengan isolat manggis dalam transfersom dan mengukur ukuran partikel dan persen penjebakan bahan aktif. Rasio yang digunakan adalah F1 (60:40), F2 (50:50), dan F3 (95:5). Setelah dioptimasi, formula dievaluasi untuk efisiensi penyerapan dan stabilitas fisik selama penyimpanan. Penelitian ini membuat transfersom dari isolat mangostin dengan metode vortexing-sonikasi dan homogenizer. Ukuran partikel diukur dengan alat analisis ukuran partikel dan efisiensi penyerapan dengan spektrofotometer UV-Vis. Hasil penelitian menunjukkan bahwa formula transfersom terbaik adalah F2 (50:50), dengan ukuran partikel 433,2 nm, PDI 0,399, zeta potensial -2,43 mV, dan efisiensi penjerapan 99,08%. Transfersom ini berpotensi sebagai sistem penghantaran isolat mangostin yang efisien ke dalam kulit dan dapat disimpan dengan lebih baik pada suhu dingin.

Key words: Transferom, vortexing-sonikasi, isolat manggis

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1. Introduction

Alpha mangostin (α-mangostin) as isolates of *Garcinia mangostana* L have high antioxidant activity as a DPPH radical scavenger[1]. Mangosteen rind mainly contains xanthones, namely α-mangostin, and other secondary metabolites such as flavonoids, and tannins[2].

The delivery of active ingredients in cosmetic products used topically is often used, yet transdermal delivery for systemic action is relatively new, and research in this field is currently developing very quickly. The transdermal route may deliver compounds with low solubility in water and those with low oral bioavailability. Further, it is a non-invasive drug delivery route through the skin or epidermis, dermis, and other layers into the systemic circulation[3].

The main problem with this transdermal active ingredient delivery system is that it has a layer, the stratum corneum, that makes it difficult for molecules coming from outside to penetrate. This layer is tightly packed, making it difficult to penetrate the skin, which can hamper the transdermal route[4]. Transfersomes are more advantageous than the liposome system as a nanovesicle system because they can penetrate the skin with smaller pores. Transfersomes can deliver drugs with various solubility properties and have elastic properties that allow them to pass through gaps 5 to 10 times smaller in size without losing their shape[5].

The components that formq transfersomes consist of phospholipids in the form of phosphatidylcholine as a vesicle-forming component, surfactants as edge activators that function to increase the flexibility of the transfersomes, and buffer solutions as a hydration medium. The composition of phospholipids and surfactants is a variable that can affect the optimisation of the transfersomes formula[6,7]. Therefore, this research was carried out to determine the most stable and better formula based on its characterisation and determine the effect of storage at different temperatures.

1.1. Materials and Methods

The mangostin (*Garcinia mangostana* L.) isolate used was from….., Apa bahan pure mangostin isolate yang digunakan untuk menghitung persen adsorbtion? soybean lecithin, Tween 80, methanol pro analysis, phosphate buffer pH 7.4, and distilled water. We also used analytical balances, a particle size analyser/zetasizer (Horiba®, japan), homogeniser, Ostwold viscometer , pH meter (Mettler Toledo, Germany), and a UV-Vis spectrophotometer (Genesys 10S Uv-Visible, Thermo Scientific, New York, NY, USA).

1.2. Preparation of Mangostin isolates Transfersomes

Optimization of the transfersomes formula was carried out using the vortexing-sonication method using a homogenizer. The components for the transfersomes were soy lecithin and tween 80 as the surfactant. Variation of soy lecithin and tween 80 were prepared to obtained the optimum formula. Soy lecithin and tween 80 were mixed first, then 0.001 gram of mangostin isolate was added, followed by 100 ml of hydrated with phosphate buffer pH 7.4. Hydration was carried out to form a lamellar structure that formed a ball-like bilayer. To do the mixing and reduce the size of the vesicles formed, ultra turrax™ homogenizer is needed at 8000 rpm for 30 min. Following, an evaluation

was carried out with transfersomes storage, including storage temperatures (<25˚ C and at >25˚ C). The formulation optimisation of transfersomes from mangosteen isolates is listed in Table 1.

Table 1 Transfersomes Formula

Formula	Soybean lecithin: tween 80
1	60:40
2	50:50
3	95:5

1.3. Particle Size Distribution and Polydispersity Index

Particle size distribution is an important factor in nanoparticle preparations. The test is determined using a particle size analyser (PSA). The PSA was used with the Dynamic Light Scattering (DLS) method at 25 ^{o}C that utilizes the principle of Brownian motion, in which the particles and molecules of a dissolved sample are in constant random thermal motion[8].

Polydispersity index

The polydispersity index is a parameter that shows the homogeneity and uniformity of particle sizes in a nanoparticle preparation. A polydispersity index value of <0.5 has a homogeneous size distribution range or indicates a homogeneous vesicle with high physical stability. The closer the polydispersity index value is to zero, the vesicle size will be more homogeneous[9].

1.4. Zeta Potential

This zeta potential measurement was carried out to predict the stability of the dispersion formula. Preparations in the form of nanoparticles with a zeta potential value of <-30 mV and >30 mV have higher stability because the particles in the dispersion system also have a zeta potential value of <-30 mV and/or >30 mV and a mutual repulsive force, and thus no tendency to merge and flocculate[10].

1.5. Adsorption Efficiency

The levels were calculated using the UV-Vis Spectrophotometric calibration curve, constructed from a pure mangostin isolate at serial concentrations of 5, 10, 15, 20, 25, and 30 ppm. The equation of each concentration series was calculated with the maximum wavelength of mangosteen isolate obtained using a Uv-Vis spectrophotometer, from which a linear regression equation was determined.

The adsorption efficiency (EP) test was carried out with centrifugation ultracentrifugation to separate the active mangostin isolate, which was not adsorbed. Speed was set at 6000 rpm for 30 min. After the supernatant and precipitate were formed, the free mangostin isolate was obtained from the supernatant, and the absorption was measured using a Uv-Vis Spectrophotometer. Drug levels were determined using the absorbance data obtained[11]. The adsorption efficiency (% EP) was calculated using the following formula:

$$\%\ EP = \frac{TD - FD}{TD}\ x\ 100\%$$

where TD is the total compounds contained in the formula and FD is the number of compounds detected in the supernatant (not adsorbed).

1.6. Evaluation of Transfersomes Preparations

The evaluation was conducted by organoleptic observation to determine the physical properties of the preparations, including shape, color, and odor to evaluate whether physical changes occur during storage. The pH of the preparation was measured using a pH meter calibrated using standard buffers (i.e. pH 4, pH 7, and pH 9) at room temperature. The viscosity was determined using an Ostwald viscometer.

2. Result

Optimization of the transfersomes formula was achieved by comparing the concentrations and differences in the temperature storage (at <25 ˚C and >25˚C) to determine a good and stable base for storage. Transfersomes were made based on the comparison of the concentrations of phosphatidylcholine and Polysorbate 80 used. The transfersomes were evaluated on days 0, 4, 7, 14, 21, and 28 at the various storage temperatures. The organoleptic properties of the transfersomes stored at room temperature on day 4th in formulas F1 to F3 showed precipitates. Similarly, the transfersomes stored in the climatic chamber produced sediment, while the transfersomes stored at low temperatures showed stable results for formulas F1 and F3 but on the 18th day and with the appearance of plaques, except for the formula F2.

Figure 1. Preparation of Transfersomes

The results of the pH evaluation of the transfersomes stored at different temperatures did not show significant changes in pH, resulting in an average pH of 6–7. The conditions set in this study allowed the skin to adapt to the pH of 4.5–8

of the preparation[15]. The viscosity of the transfersomes produced an average value of 0.74 cP, which is influenced by the relationship between the length of the flow time; the longer the flow time, the greater the viscosity of a liquid, while the shorter the flow time, the lower the viscosity and size of the liquid. Therefore, the F2 formula with a 50:50 ratio was chosen to be added to the mangostin isolate at 0.001 gram/mL.

3. Discussion

Transfersomes preparations are used as a delivery medium through the skin. The manufacturing method used for mangostin isolate-transfersomes preparations used vortexing-sonication or the direct stirring method. This method can produce transfersomes isolates of mangosteen that tend to have better physical stability and particle size. This method can assist in producing a more uniform transfersomes structure with a smaller particle size[16].

From the analysis of the transfersomes preparations using the PSA and measured in triplicates, the results were obtained in the form of PDI data or polydispersity index, which indicates the homogeneity of the particle size distribution. The smaller the resulting PDI value or close to zero, the more uniform the particle size distribution is[14,] while the Z- Average indicates the average particle size produced. Based on the Z-Average data, the particle size in the transfersomes F2 produces a value of 433.2 nm ±SD (Figure 2). The results of the measurements performed show that the transfersomes vesicle meets the transfersomes requirements for a vesicle size range of 100–400 nm, which is included in the large unilamellar vesicle (LUV) category[4].

The vesicle size of the transfersomes is also affected by the particle size reduction that used an ultraturax homogenizer at 8000 rpm because it is influenced by higher speeds and produces greater frictional forces and more efficient breakdown. Likewise, the results of the polydispersity index test yielded a value of 0.399 (Table 2). If the polydispersity index value produces a value of <0.5, then vesicles are homogeneous with high stability.

Table 2. Transfersomes Particle Size Distribution and Polydispersity Index of F2.

No of Testing	Size(nm)	Polydispersity Index
Testing 1	426.5	0.394
Testing 2	437.1	0.415
Testing 3	436.1	0.390
Average	433.2	0.399

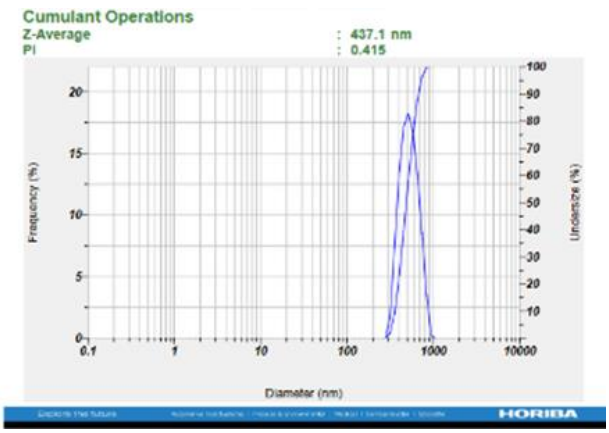

Figure 2. Particle size distribution of the transfersomes produced

The zeta potential measurement was used to determine the stability of the preparation against storage conditions and to know the ability of particles to aggregate again increasing the particle size[16]. The particle may be stable if it has a potential value of >30 mV or >-30 mV in the presence of repulsive forces between particles with the same charge that can avoid aggregation and avoid combination to form larger particles. Based on the zeta potential obtained, formula 2 produced a value of -2.43 (Table 3 and Figure 3).

Table 3. Transfersomes Zeta Potential.

Formula 2 Testing	Zeta Potential (mV)
Testing 1	-2.7
Test 2	-2.3
Testing 3	-2.3
Average	-2.43

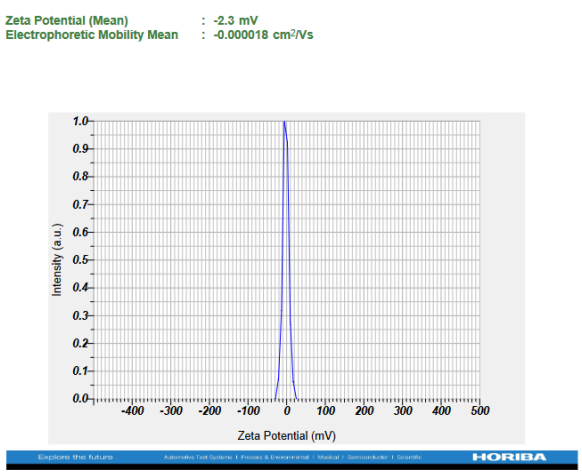

Figure 3. Zeta Potential Measurement

The entrapment efficiency test was carried out to determine the effect of the concentration of the active substance on its adsorption in the vesicles. Adsorption efficiency can be used as the main parameter in determining the formula for the manufacturing of nanovesicles. The amount of free mangostin isolate was separated using ultracentrifugation at 6000 rpm for 30 min. The absorbance of the supernatant resulting from centrifugation was measured using a spectrophotometer to determine the level of mangostin isolate that was not absorbed. The results of the equation from linear regression were: y=0.0535x - 0.022 with a mark coefficient correlation of 0.97.

The measurements of mangostin isolates that were absorbed in the transfersomes showed a 99.08% yield. The requirement for adsorption efficiency in transfersomes was not <60%, showing that the research carried out on transfersomes preparations containing mangostin isolate met the requirements because it was >60% with an adsorption efficiency level of 99.08%. The higher the adsorption efficiency value, the higher the skin penetration ability and the smaller particle size. Further, it can increase the flexibility of the lipid bilayer membrane, thereby allowing the transfersomes to pass through pores that are smaller than the size of the vesicle spontaneously.

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Transfersomes isolate mangostin produced was yellowish-white in colour. The resulting colour was due to the active ingredients used, namely mangostin isolate and soy lecithin. These transfersomes had a characteristic smell of lecithin. The transfersomes that were stored at low temperatures did not settle or no separation occurred, whereas transfersomes that were stored at low temperatures in the climatic chamber had sedimentation within the first week

The results of the pH testing in the formulas obtained with two storage temperatures (i.e. cold temperatures and climatic chambers) show that the pH testing produced values in the range of 6–7.

Viscosity was determined using an Ostwold viscometer. It is important to measure viscosity because it shows the resistance of a liquid to flow. The factors that affected the viscosity included the mixing or stirring process during the preparation, and the selection of thickeners and surfactants used. The viscosity measurements on transfersomes preparations containing mangostin isolate during week 0 to week 4 were in the range of 4–8 cps. The difference in flow viscosity was related to the presence of suspended particles.

4. Conclusions

A mangostin isolate was used in transfersomes preparations as an active substance. Mangostin isolates must be able to penetrate the skin and reach subcutaneous adipose tissue as its target. The entrapment efficiency value obtained from the UV-Vis Spectrophotometer method showed that the entrapment efficiency value of the mangostin isolate was 99.08%. The storage results of transfersomes preparations stored at < 25˚C and >25˚C for one month showed that the transfersomes preparations stored at cold temperatures show organoleptically more optimal preparations.

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