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Spray Drying of Asiatic Acid-Palm Oil in Maltodextrin: Improving the Nanoemulsion Characteristics

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Abstract

Combination of Asiatic acid (AA) and palm oil (PO) is promising to be developed. However, both have low solubility, low absorption, rapid metabolism, low bioavailability, and high oxidation which need to be improved in order to provide good activity. Thus, nanoemulsion formulation followed by spray drying were optimized to enhance the physical and chemical characteristics of the products. Lecithin (L), poloxamer188 (P), span80 (S), tween80 (T) were used as surfactants to form nanoemulsion and maltodextrin (M) was used as spray dried matrix component. Different amounts of maltodextrin were optimized at low (M1), medium (M2), and high (M3) levels. Characterization and evaluation were carried out on products, including particle size, morphology, product recovery (yield), drug content, solubility, and dissolution rate. The characterization results showed that nanoemulsion was successfully prepared and spray dried microparticles with a good physical form were obtained. The microparticles could be rapidly redispersed to form size of 149.0 – 271.1 nm with the zeta potential value lower than -30mV. Both physical and chemical stability of the microparticles showed no significant difference after 6-month storage. Lecithin-Tween-medium Maltodextrin (LTM2) formula showed the most optimum results with good physical characteristics and a high dissolution rate. In vitro release profile of LTM2 showed area under the curve (AUC) and dissolution efficiency at 180min values of 14725.10 ± 480.60 and 81.81 ± 2.67%, respectively. It could be concluded that spray dried microparticles of AA-PO nanoemulsion formulation improved the physical and chemical characteristics of both compounds presumably suitable good bioavailability and activity.

Keywords: *Asiatic acid, Palm oil, Spray dry, Nanoemulsion, Maltodextrin.*

1. INRODUCTION

Asiatic acid (AA) can be obtained from *Centella asiatica*, a tropical medicinal plant in the family of Apiaceae widely found in Asia, Africa, South America, and Oceania [1, 2]. AA has already known as potential antitumor, antihypertensive, antimicrobial and neuroprotective agent [3]. In terms of physicochemical and pharmacokinetic characteristics, AA has limits in its therapeutic application. The key issues to be developed from AA are solubility, lipophilicity, absorption, metabolism, elimination rate, and bioavailability. Due to poor absorption and rapid metabolism by CYP450 enzymes in the liver. This is aggravated by AA poor solubility in aqueous solutions, resulting in very low oral bioavailability to be effective as an active substance. Several dosage forms, including nanoparticles, transdermal, multiple emulsions, liposomes, and solid dispersion complexations, can be used to improve AA delivery and reduce the limitations [3].

Meanwhile, palm oil (PO) is a vegetable oil derived from the *Elaeis guineensis* plant (family of Arecaceae) that is high in

vitamins A and E but lacks lipid-raising fatty acids (myristic acid) due to its high saturated fatty acid concentration [4, 5]. It provides benefits as an antioxidant and synergistic effect when combined with AA such as reducing the risk of arterial thrombosis, atherosclerosis, and wall-thickness, which will synergize the antihypertensive action of AA. However, its ease of oxidation is a limitation. The half-life and vitamin content of PO may be reduced as a result of this oxidation. The encapsulation technique, which shields the substance inside the system, is one method chosen to avoid oxidation [6, 7].

Nanoemulsion is a dosage form that can be manufactured for the purpose of nanoencapsulation. The oil phase is emulsified into tiny droplets using an emulsifier [8]. The production technique used in this research employed a high-energy approach combined with an ultrasonication procedure. Parameters in the manufacturing process (energy and production time) had been optimized and consistently established in different formula. Nanoemulsion can be considered as a candidate for AA formulation because of its benefits, such as superior physical stability, better solubility, and increases bioavailability [8]. The emulsifying agent is required in the nanoemulsion component because it reduces the interfacial tension between the oil and water phases and prevents agglomeration [9]. Poloxamer188, span80, and tween80 are non-ionic surfactants which are not affect the zeta potential of the system formed and have been known to be able to maintain the nanoemulsion physical stability with extract or isolate as the active substance [10, 11, 12]. Meanwhile, lecithin derived from soybean that also has the ability as a surfactant [13], was chosen as an alternative of natural substance. They were used in this research to maintain the physical stability of the nanoemulsion.

Nanoemulsion can be dried with a spray drier to decrease the chance of oxidation [14]. Spray drying produces an enclosed system that keeps the active substance and prevents the Oswald ripening event from causing aggregation [15]. Maltodextrin and magnesium stearate were employed as carriers and lubricants to keep the product thermodynamically stable. Maltodextrin in spray drying process is capable of drying oil-in-water emulsions with active ingredients of oil and natural substances, such as carotenoids and *Moringa oleifera* oil, increases their bioavailability and oxidative stability [16, 17, 18].

The goals of this study are to enhance the properties of AA and obtain an optimal AA-PO dry product. The selected formula was determined based on the most optimal physical properties, solubility, dissolution rate, and physical-chemical stability. Success in improving the physicochemical characteristics of AA-PO presumably indicates to increase its bioavailability and activity of the combined compounds for further study.

2. EXPERIMENTAL

2.1. Materials

AA (≥ 95%) used in the formulation was supplied by New Natural Biotechnology Co., Ltd, (Shanghai, China); and PO was from Sigma-Aldrich (St. Louis, Missouri, USA). Pharmaceutical grades excipients used in the study such as span 80 and magnesium stearate were provided by S. Tong Chemicals (Nonthaburi, Thailand), kolliphor® poloxamer188, soy lecithin, and maltodextrin from Sigma-Aldrich (St. Louis, Missouri, USA), while tween80 was provided by Maximax Pro Co., Ltd (Bangkok, Thailand). Other materials such as Triton X-100® was supplied by Calbiochem, Merck Millipore Co., (Darmstadt, Germany), absolute ethanol from Emsure, Merck Millipore, Co., (Darmstadt, Germany), acetonitrile and methanol in HPLC grade were supplied by Chemical Express Co., Ltd (Samutprakarn, Thailand), hydrochloric acid and tribasic sodium phosphate were from Merck Millipore Co., (Darmstadt, Germany).

2.2. Preparation of Nanoemulsion

AA nanoemulsion preparation was carried out in both aqueous and oil phases. Span80, lecithin, poloxamer188, and tween80 were utilized to reduce the interfacial tension between the oil and water phases in an optimum ratio. The preparation process was done by combination of high speed homogenization and ultrasonication [19, 20].

The procedure began with the melting of 1 g PO from storage in 70^{o}C and the addition of 1 g oil phase surfactant, namely lecithin for lecithin-poloxamer-maltodextrin (LPM) and lecithin-tween80-maltodextrin (LTM) formula, while span80 used for span80-poloxamer-maltodextrin (SPM) formula. AA, on the other hand, was weighed 0.2 g, dissolved in 9.8 mL ethanol, and mixed into the oil phase. Pre-homogenization began with a low speed (5,000 rpm), the water phase was then applied dropwise to the oil phase in the glass beaker (consisting of 0.3 g poloxamer or tween80 surfactant, and deionized water). The speed of the ultraturrax (IKA T25 digital, Thailand) was then increased to 10,000 rpm for 5 min. The preparation was then proceeded by homogenizing the AA nanoemulsion with a probe sonicator (Sonics Vibra-cell, USA) for 7 min at 13 W pressure and 60 percent amplitude.

2.3. Spray Drying of Nanoemulsion

After the nanoemulsion was formed and kept for approximately 5 days, the spray drying process was carried out. Critical parameters of the spray dryer (Buchi B-290, Germany) such as inlet temperature, aspirator rate, pump flow, and nozzle clean were maintained continuously in this process to create a high yield and repeatable product [14, 21]. Maltodextrin and 0.055 g magnesium stearate was added as a carrier and lubricant, respectively before spray drying. Maltodexrin was weighed 1.945 g, 2.945 g, and 3.945 g as low (M1), medium (M2), and high (M3) amount, respectively, and then dissolved in 7 mL of hot deionized water previously. The maltodextrin solution and magnesium stearate were then poured into the nanoemulsion while being constantly stirred at 5,000 rpm. The mixing process was continued for 5 min and the mixture was spray dried. Airflow and aspirator rate were set at 40% and 90%, respectively. The inlet temperature used in the process was 70^{o}C, and the solution flew at 5.5 mL/min.

2.4. Characterization of Asiatic Acid Nanoemulsion and Microparticle

2.4.1. Particle Size, Distribution, and Zeta Potential

Particle size measurement was performed using both the wet and dry methods. The Zetasizer (Malvern Instruments Nano ZS®, UK) with zetasizer capillary cells (Malvern DTS 1070, UK) were used to evaluate the size, size distribution, and zeta potential of nanoemulsion and redisposed micro-encapsulate droplets. The determination of this instrument was based on complex light scattering and electrophoresis. To avoid multiple scattering effects during analysis, all samples were diluted to a 1:100 ratio in deionized water before measurement. Triplicate measurements were taken to ensure repeatability [22]. The droplet size (z-average diameter), size distribution in polydispersity index (PDI), and zeta potential were used to characterize the results of this assessment [23].

Meanwhile, dry products were tested using morphologically-directed Raman spectroscopy (MDRS) (Malvern Morphologi 4-ID, UK) using the dry process. Dry powder of pure AA and microparticles were spread on a glass plate at 3 bar of air pressure and analyzed at the calibrated condition and appropriate magnification. The mean particle size, D90, D50, and D10 values were obtained from these observations. Span value was measured from D90, D50, and D10 to indicate particle size distribution, with a broader span value indicating a broader size distribution [24]. The sample span was defined by (D90 – D10) and divided with D50.

2.4.2. Particle Shape and Morphology

Scanning Electron Microscope (SEM) **(**Jeol JSM-IT-500HR®, Japan) was used to observe the structure and morphology of pure materials, physical mixtures, and microparticles at 10 kV and 10 mA. Samples were first adhered to a double-sided adhesive carbon tape before being sputtered with gold for 3 min. Then, several pictures with different magnification were taken and analyzed.

The morphology of AA nanoemulsion and redispersed nanoparticle was observed with a Transmission electron microscope (Jeol JEM-2100, Japan) at 80 kV. Approximately 5 µL of diluted nanoemulsion (1/100) was dropped onto 3 mm carbon film coated copper grid and stained with 1% phosphotungstic acid solution before being analyzed. Image result was used in comparing the particle morphology and shape changes during production.

2.5. Total Product Recovery (Yield)

The total product recovery (PR) was obtained from the spray drying process. It was an essential for determining the formulation process efficiency [25]. PR was calculated with the equation below as percentage value.

$$\text{PR} = \frac{\text{collected product} - \text{powder mass}}{\text{total mass of solid in the feed}} \text{ x } 100\%$$

2.6. Asiatic Acid Content

Samples were weighed accurately and dissolved in methanol. AA concentration was evaluated using high-pressure liquid chromatography (HPLC) (Agilent 1260 Infinity II, USA) and calculated from the calibration curve (R^2 0.999). HPLC column Halo® C18 5 µm 90Å (250 x 4.6 mm) (Applied Chemical and Instrument Co., Ltd., Bangkok, Thailand) was used in the evaluation. The mobile phase of acetonitrile: water (45: 55) was used with a flowing rate of 1mL/min. Each observation used 20 µL injection volume of sample, and AA peak was seen at a wavelength of 205 nm with UV detector. Prior to injection, the sample was diluted in methanol based on the concentration range on linearity curve, and filtered with 0.45 µm filter. With the HPLC assay condition used, the sample peak was seen at the retention time around 8.30 to 8.50 min. Each sample was examined 3 times, and the mean values were calculated. AA was calculated as percentage ratio of AA mass in sample to total sample mass. AA content measurement replication used product and physical mixture at different sampling points to ensure product uniformity and homogeneity during the mixing and drying process.

2.7. Moisture Content

Moisture content was evaluated with a moisture balance (Mettler Toledo HR83, Germany) by comparing the weight difference in the pan before and after the drying process with halogen lamp heat. The temperature used for drying was increased to 105°C, and kept constant until the sample stable weight was reached [26, 27].

2.8. Spray Dried Microparticle Stability

Asiatic acid dry microparticles were stored in the sealed glass bottle and kept in the climatic chamber (Binder KBF720, Germany). The climatic chamber temperature and relative humidity were set at 40 ± 2°C and 75 ± 5%, respectively. The sample were kept up and evaluated at 0, 3 and 6 months. The physical stability was analyzed from the particle size, span value and moisture content changes; while Asiatic acid content was used to determine the chemical stability.

2.9. Solubility Test

The solubility of AA was analyzed by adding much amount of sample to 10 ml of deionized water. The suspension was then shaken at 100 rpm, 25°C for 24 hr in shaking incubator (LabTech LSI-3016R, China) until saturation solubility was achieved. The suspension was then filtered via a 0.22 µm syringe filter. The resulting filtrate was a saturated AA solution. The

concentration of AA was then measured using HPLC with the validated assay technique as mentioned in the AA content assay. The value was calculated based on the area and calibration curve. The experiments were carried out in triplicate, and the mean data were obtained.

2.10. In-Vitro Release Profile

AA dissolution profile was accomplished in simulated gastric without pepsin and intestinal fluids with a dissolution tester (Vankel VK 7000, USA). AA release profile was determined using the paddle method [28, 29] with modification. For the first 2 hr, the medium was 112.5 mL of 4% Triton X-100® in 0.1 N hydrochloric acid, and then 37.5 mL of 4% Triton X-100® in 0.20 M tribasic sodium phosphate solution was added to change the pH from 1.2 to 6.8 ± 0.05 for the remaining 1 hr.

Pure AA, microparticle, and its physical mixture (equivalent to 10 mg AA) were placed in gelatin capsules and put into the simulated fluids with a sinker, which was kept at 37 ± 0.5°C with 100 rpm stirring. After 5, 15, 30, 60, 120, 150, and 180 min, two mL of fluid were withdrawn and replaced with new simulated gastric or intestinal fluid. To eliminate undissolved particles, samples were filtered using a 0.45 µm pore size filter. Following that, samples were diluted with methanol. The concentrations of AA in the samples were measured by the validated HPLC assay method.

2.11. Statistical Analysis

The resulted data was calculated as triplicate and presented in mean ± deviation. The statistical significance was obtained using one way ANOVA in Graphpad Prism Version 9.4.0. A p-value < 0.05 declared as statistically significant. While qualitative tests, such as physical appearance and particle shape were determined using descriptive.

3. RESULTS

3.1. Physical Appearances

The preparation process succeeded in obtaining the product as expected. In Figure 1, it could be seen that the nanoemulsion was formed and was physically stable during the initial storage. PO as the oil phase can disperse AA well. Meanwhile, lecithin, span80, poloxamer188, and tween80 as surfactants managed to keep the nanodroplets homogeneous in the aqueous phase.

After 5 days of evaluation, the nanoemulsion was then dried using a spray dryer. Maltodextrin as a carrier succeeded in encapsulating the material to form a microparticle matrix as shown in Figure 1. Physically good organoleptic microparticles were successfully formed. These microparticles were used in the subsequent evaluation.

The morphology of the particles and droplets formed were shown in Figure 2. Droplets and particles in nanoemulsion, spray-dried microparticles, and redispersed nanoparticles showed a relatively spherical shape. The addition of maltodextrin as a hydrophilic carrier resulted a change in the appearance of the droplet with a brighter core than before the spray drying process, as seen in the TEM results (Figure 2c).

3.2. Characterization of Asiatic Acid Nanoemulsion and Microparticle

3.2.1. Particle Size, Distribution and Zeta Potential

Figure 3 shows the particle size, polydispersity index, and zeta potential of nanoemulsion and dispersed microparticles with the wet method. Meanwhile Figure 4 shows the particle size and span value of microparticles using the dry method. The droplet particle size ranged from 181.6 – 271.1 nm with a polydispersity index value of not more than 0.399 which indicated that a homogeneous nanoemulsion had been formed. The nanoemulsion also successfully maintains its physical stability for up to 5 days by delaying the formation of agglomerates as seen in minimum or no changes in the nanoemulsion profile on the fifth day according to Figure 3.

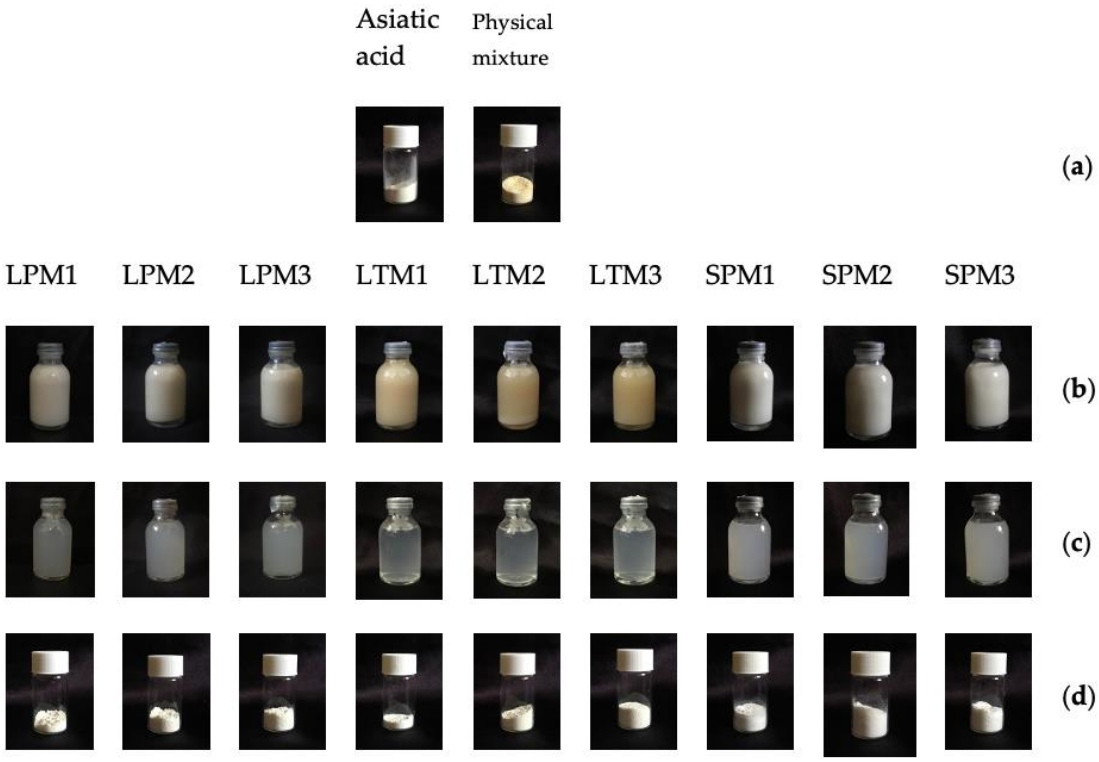
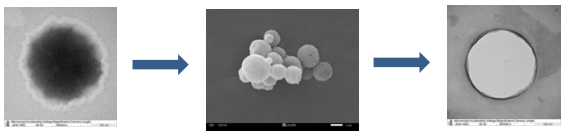


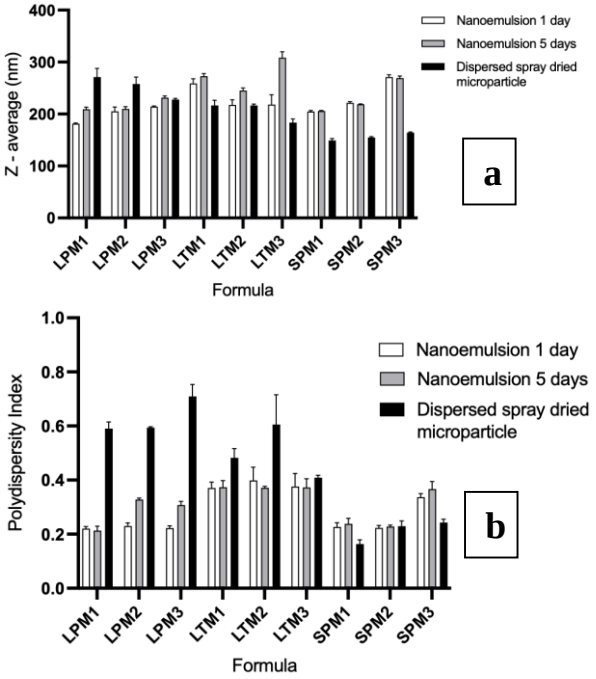
Figure 1. *Physical appearances of asiatic acid, physical mixture, and all formulas in several forms: (a) Powder; (b) Nanoemulsion; (c) Dispersed nanoemulsion in 1:100 ratio; and (d) Spray-dried microparticle.*



(a) (b) (c)

Figure 2. *Droplet or particle morphology determined by SEM and TEM; (a) Nanoemulsion droplet with 300,000x magnification by TEM; (b) Spray-dried microparticle with 10,000x magnification by SEM; and (c) Redispersed nanoparticle droplet with 300,000x magnification by TEM.*

The formed microparticles also showed lower particle size and span value than AA powder (6.05 μm). Moreover, the zeta potential of nanoemulsions and microparticles obtained was beyond -30 mV. It could be assumed that stable products were formed with high resistance toward particle aggregation. The negative charge of nanoemulsion was probably due to the presence of free fatty acids. The decrease in zeta potential value of the microparticles could be due to the success of maltodextrin as a non-ionic carrier in the spray drying process to encapsulate nanoemulsion including their free fatty acid components.



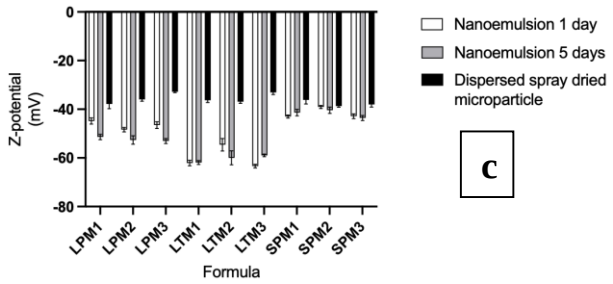


Figure 3. *Zetasizer wet method result of nanoemulsion and dispersed spray-dried microparticle: (a) Particle size (b) Particle distribution; and (c) Zeta potential.*

In Figure 4, LPM showed a smaller particle size of microparticles, while LTM microparticles had a more homogeneous particle size. However, when dispersed in water, all microparticles immediately redispersed with a size of 149.0 – 271.1 nm. This result showed that the surfactant had also succeeded in forming spray-dried microparticles with a more controlled particle size than pure AA, and immediately dispersed into nanosize in water.

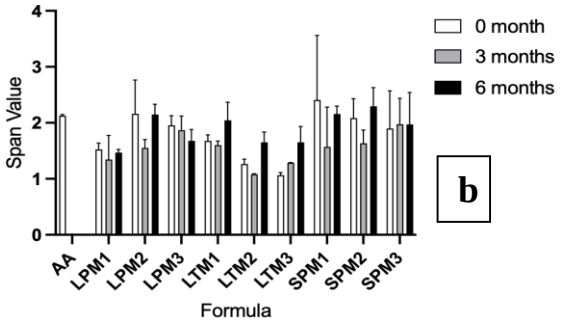
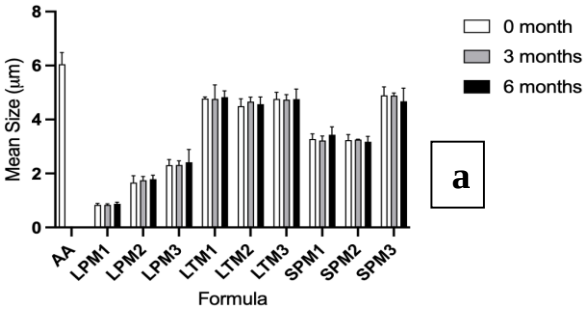


Figure 4. *Dry method particle characterization of spray-dried microparticle: (a) Mean particle size (b) Span value of particle distribution.*

3.2.2. Particle Shape and Morphology

The particle shape and morphology of the raw material, physical mixture, and final product are shown in Figure 5. Heterogeneous size and shape of physical mixture of AA with a larger excipient. However, nanoemulsion formulation followed by spray drying process has succeeded in forming microparticles with spherical or almost spherical shapes with and smooth surface.



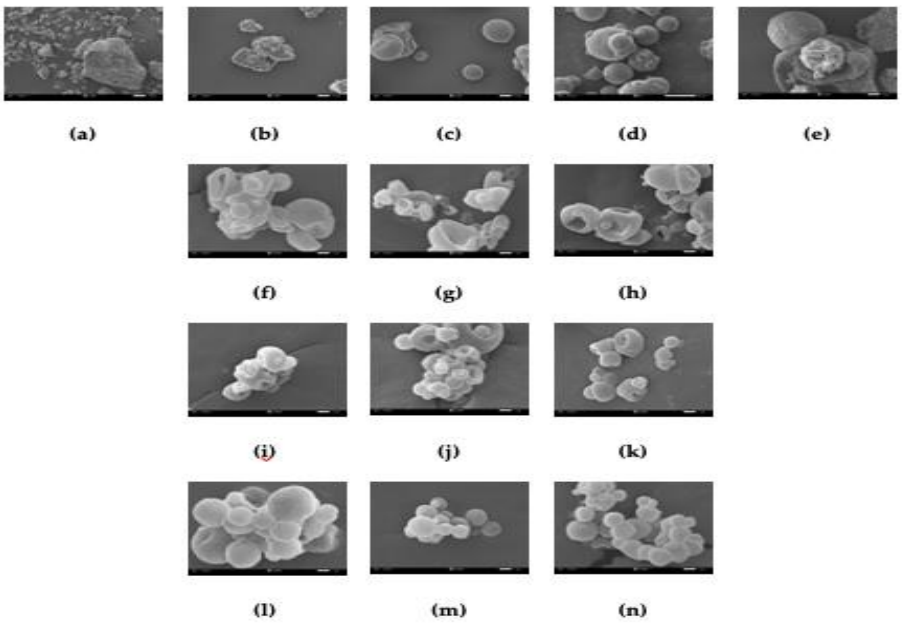


Figure 5. *SEM result of raw materials, physical mixture and spray dried microparticle: (a) Asiatic acid (b) Lecithin and (c) Maltodextrin in 1000x magnification; (d) Poloxamer 188 in 50x magnification; (e) Physical mixture in 1000x magnification; (f) LPM1 (g) LPM2 (h) LPM3 (i) LTM1 (j) LTM2 (k) LTM3 (l) SPM1 (m) SPM2 and (n) SPM3 in 10,000x magnification.*

3.3. Total Product Recovery (Yield)

The production process involved homogenization, sonication, and spray drying. The product recovery obtained was shown in Figure 6.

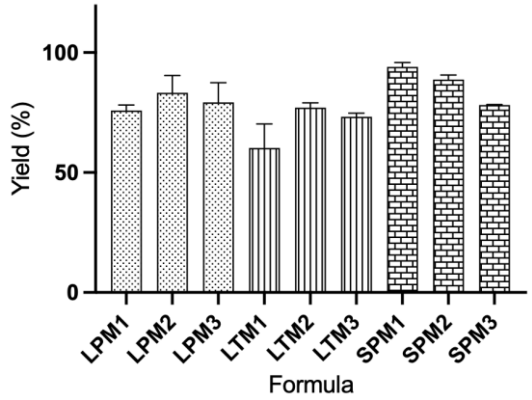


Figure 6. *The yield of microparticle product after formulation.*

LTM1 yield was minimum because low amount of maltodextrin caused a certain amount of mass to adhere to the walls of the drying chamber and cyclone, thus lowering the amount of dry product that could be accommodated in the collector. Meanwhile, in other formulas with the addition of higher amount of maltodextrin and the use of poloxamer 188 as a surfactant, the yield was quite high of > 70%.

3.4. Asiatic Acid Content

AA content in microparticles was determined chromatographically, and the results are shown in Figure 7.

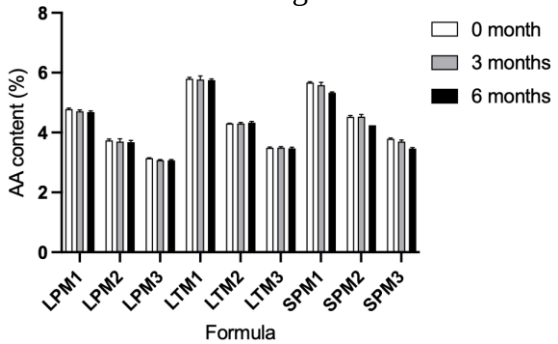


Figure 7. *Asiatic acid content in the microparticle dry product.*

The AA content value was equal to the amount of drug used in each formula. The results from all 9 microparticles formulas were in the range of 3.14 – 5.80%.

Observations for 6 months were used to see the chemical stability of AA in the storage under accelerated conditions. It was seen that there was no significant change in the results of the third and sixth-month analysis. The change did not exceed 5% from the initial value which indicated that the microparticle system could maintain the stability of AA storage in air-tight conditions.

3.5. Moisture Content

Figure 8 shows the results of observing the moisture content of 9 formulas for 6 months in air-tight storage.

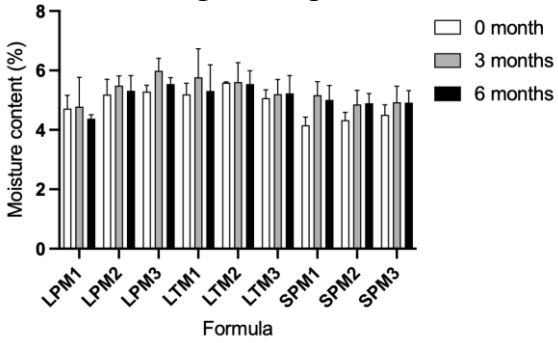


Figure 8. *The moisture content of microparticles in 0, 3, and 6 months of storage.*

The moisture content value obtained was quite good ranging from 4.16 to 5.99%. There was no significant change in value during storage so the tendency for the formation of agglomerates of higher particle size was minute.

3.6. Solubility Test

Solubility of AA in deionized water was analyzed after being shaken for 24 hr. The result of the solubility test can be seen in Figure 9. Higher solubility was obtained in all formulas. Lecithin, tween 80, and maltodextrin as excipients formed micro-

particles with the highest AA solubility, which was 25 – 31 times compared to the AA powder form. The result also showed that poloxamer188 as a polymer in the formula could form microparticles with good physical characteristics. However, its presence in the surrounding of AA inhibited the diffusion of water to contact and dissolve AA from the system.

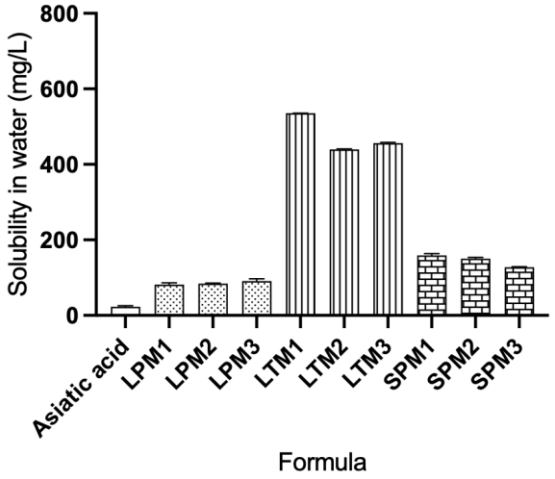


Figure 9. *Solubility data of asiatic acid in deionized water (mg/L).*

3.7. In-Vitro Release Profile

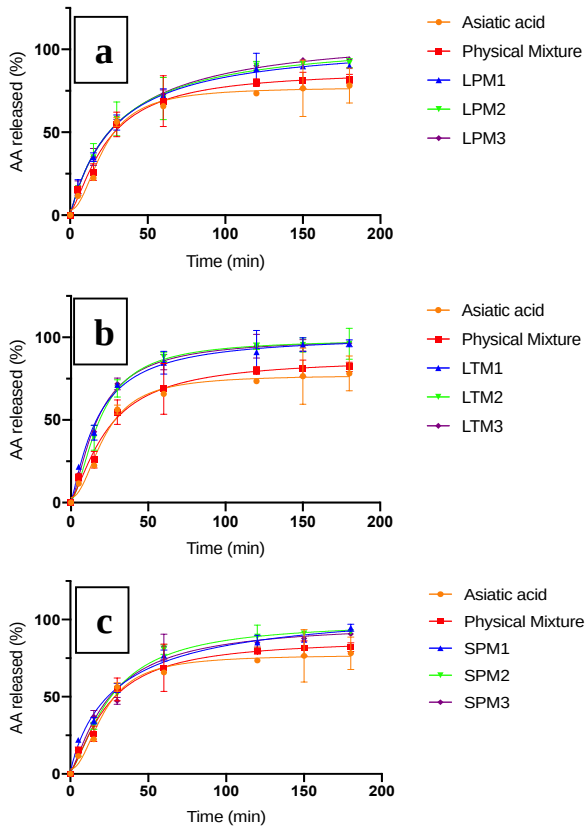


Figure 10. *Asiatic acid released profile in powder, physical mixture, and microparticle form: (a) AA in LPM; (b) AA in LTM; (c) AA in SPM.*

The in-vitro release profiles of AA are shown in Figure 10. It can be seen in Figure 10 (b) that AA acid in the system formed with lecithin, tween80, and maltodextrin had the highest dissolution profile compared to AA powder and its physical mixture and compared to other formulations in Figure 10 (a) and Figure10 (c). This was corresponding to the solubility data of AA in microparticles shown in Figure 9.

Table 1. *The area under the curve (AUC) and dissolution efficiency (DE) of asiatic acid at 180 minutes.*

Formula	AUC	DE 180 (%)
Asiatic acid	11392.54 ± 649.89	63.29 ± 3.61
Physical mixture	12066.37 ± 1388.67 [a]	67.04 ± 7.71 [a]
LPM1	13122.29 ± 244.50 [b]	72.90 ± 1.36 [b]
LPM2	13230.40 ± 584.22 [b]	73.50 ± 3.25 [b]
LPM3	13392.50 ± 123.65 [b]	74.40 ± 0.69 [b]
LTM1	14557.00 ± 784.13 [c]	80.87 ± 4.36 [c]
LTM2	14725.10 ± 480.60 [c]	81.81 ± 2.67 [c]
LTM3	14703.18 ± 872.81 [c]	81.68 ± 4.85 [c]
SPM1	13190.94 ± 350.36 [b]	73.28 ± 1.95 [b]
SPM2	13431.97 ± 356.72 [b]	74.62 ± 1.98 [b]
SPM3	13186.11 ± 452.12 [b]	73.26 ± 2.51 [b]

[a] Indicates not statistically different than asiatic acid group ($p > 0.05$); [b, c] Indicates statistically different than asiatic acid group ([b] with $p < 0.05$) ([c] with $p < 0.001$)

The area under the curve (AUC) and 180 min dissolution efficiency (DE) of AA value are shown in Table 1. LTM2 obtained higher AUC and DE values of 14725.10 ± 480.60 and 81.81 ± 2.67%, respectively. This result was significantly ($p < 0.001$) higher than the AUC and DE values of AA powder which were only 11392.54 ± 649.89 and 63.29 ± 3.61%, respectively.

4. DISCUSSION

Spray-dried nanoemulsion of AA has

been performed to meet some requirements of physical and chemical characteristics [16, 30]. Physical appearance, morphology, and solubility were some examples of the observed physical characteristics. PO with its ability to encapsulate compounds that are poorly soluble in water, acted as an oil phase in nanoemulsion system [31]. While span80, lecithin, tween80, and poloxamer 188, as surfactants in nanoemulsion also succeeded in forming and maintaining the stability of AA dispersion [10, 11, 13, 32]. Finally, in the spray drying process, maltodextrin satisfactorily acted as a carrier and stabilizer in encapsulating and improving the stability of AA in dry microparticles as a final product form [17, 33]. Physically, a successful formulation could be obtained by no visual changes occurring nor aggregations for 5 days of nanoemulsion observation and 6 months of storage of the microparticles. This was related to the function of the surfactant in preventing agglomeration, the zeta potential value generated and the carrier used [17]. Although, the span value of LTM1 resulted in an increasing value, indicating that the resulting particle size was increasingly heterogeneous. Low amount of malto-dextrin was unable to maintain particles to form agglomerates. The high deviation in the observation of moisture content and low yield also supported the aforementioned statement. While in other formulas, increasing the amount of maltodextrin or its combination with poloxamer 188 and span 80 could improve physical characteristics as expected.

AA as a pentacyclic triterpenoid substance was known with its low solubility and bioavailability [34]. Thus, the increase in solubility and AA release from the microparticles had an important impact. Lecithin, tween 80, and maltodextrin as matrix increased solubility up to 30.64 times. The dissolution rate also became significantly higher compared to powder or physical mixture forms. This increment was strongly influenced by particle size reduction and the use of hydrophilic polymers as surfactants and carriers which increase the wettability [21, 33]. According to the observations, it can be seen that the microparticles formed at a size of 0.833 – 4.897 µm, smaller than the average size of pure AA of 6.05 µm. In addition, dispersion of microparticles in water immediately formed nanoparticles in the range of 149.0 – 271.1 nm, supporting the previous explanation regarding to the increase in solubility and dissolution rate. A high zeta potential of more than -40 mV was estimated to be formed due to the induction of hydrocarbon functional groups owned by PO [35]. However, encapsulation in maltodextrin as a non-ionic carrier can reduce its zeta potential to the range of -33.1 to -38.7 mV, which was possible to provide steric and electrostatic resistance to maintain its physical stability. Basically, a negative charge on the surface of a particle had lower toxicity to the cell than a positive charge. However, in the zeta potential range obtained which was lower than nanoemulsion form, microparticles was safer from the toxicity possibility [35, 36, 37].

Evaluation of the microparticle was repeated until 6 months of storage in air-tight condition. Changes that occur each time of observation were relatively insignificant, indicating that the dry microparticle system formed by spray drying could maintain the stability of AA. Physically characterized by the absence of agglomeration or increase in particle size, and chemically characterized by the stability of AA content. Maltodextrin was also capable to perform as a stabilizer and wall material loaded by a thermally unstable substance. It significantly protected the drug and provided retention of heat received during the drying and storage process [33]. The results of this study indicated that the use of a combination of lecithin, tween80, and maltodextrin was promising for the next formulation modification. The success of the microparticle system modification into AA material could be continued with the dosage

form preparation and clinical study to obtain the useful dose regimentation in clinical studies.

5. CONCLUSION

In summary, physical and chemical characteristics of AA have improved by formation into nanoemulsion and the consequent spray drying. Physical appearance, particle size, zeta potential, and retention to agglomerate (physical stability) were provided with initial formulation success. Furthermore, spherical micro-particles were also successfully formed by spray drying the nanoemulsion. Maltodextrin as a carrier loaded the nanoemulsion into the dry form and maintained its physical and chemical stability for up to 6 months of storage. Satisfactory result was also seen in the solubility and in-vitro release study. The increase in solubility up to 30.64 times compared to pure AA powder in water revealed a good impact of the particle size reduction process and the use of hydrophilic polymers as surfactants and carriers of the formula. LTM2 was found to be formula with good physical characteristics and optimum dissolution rate of AA in gastric fluid to phosphate buffer pH 6.8 (with 4% of Triton X-100) medium with AUC value of 14725.10 ± 480.60 and dissolution efficiency of 81.81 ± 2.67%, respectively. These satisfactory results were promising to be continued with a production scaleup and further evaluation of its clinical activity and the required dose compared to pure AA.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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