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Stability Improvement and Solid-State of *Sauropus androgynus* Leaf Extract Solid Dispersion Using a Carrier of Polyvinylpyrrolidone

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ABSTRACT

The Sauropus androgynus leaf contains various phytochemical compounds with various pharmacological activities. However, phytochemical compounds in plant extracts are generally unstable during storage or formulation. This study aimed to prepare S. androgynus leaf extract solid dispersions and evaluate the solid-state properties and stability. Solid dispersions were produced through solvent evaporation using polyvinylpyrrolidone (PVP) as the carrier. Solid dispersions were characterized by powder X-ray diffractometer (PXRD), differential scanning calorimeter (DSC), and scanning electron microscope (SEM). Solid dispersions were stored at a temperature of 60 °C for 30 days, and the stability was determined by measuring the total flavonoid content. The preparation results showed that solid dispersions of S. androgynus leaf extract with PVP K30 and PVP K90 carriers were amorphous solids with a glass transition temperature of 160-170 °C. The phytochemical content of the extract in solid dispersion showed degradation at a temperature of 175.3 - 188.3 °C. At a temperature of 60 °C for 30 days, the decrease of total flavonoid content in solid dispersion was lower than in pure extract. Thus, the formation of solid dispersion of S. androgynus leaf extract with PVP K30 and PVP K90 carriers can increase the stability of phytochemical compounds in S. androgynus leaf extract.

1. Introduction

The *Sauropus androgynus* is a very popular plant in Indonesia. *S. androgynus* leaf is often used as vegetables daily. In the pharmaceutical field, *S. androgynus* leaf has various pharmacological activities such as antioxidants, antiobesity, antianemia, antimicrobial, analgesic, and anti-inflammatory. These pharmacological activities come from the phytochemical content of *S. androgynus* leaf, including flavonoids, alkaloids, tannins, saponins, terpenoids, and steroids (Anju et al., 2022; D'Souza et al., 2021; Purba & Paengkoum, 2022). Therefore, *the S. androgynus* leaf has excellent potential to be developed into various medicinal preparations.

The development of drug preparations from plant extracts often experiences obstacles caused by the low stability of phytochemical compounds (Durante et al., 2016; Muñoz-Shugulí et al., 2021). Many phytochemical compounds in plant extracts are easily degraded during storage and formulation (Sansone et al., 2016; Fu et al., 2021). Phytochemical compounds of flavonoids, anthocyanins, and polyphenols from red grape skin extract and sour cherry extract showed degradation, where degradation increased with increasing temperature (Oancea et al., 2017; Serea et al., 2022). Likewise, in waxy purple corn cob extract, the anthocyanin content decreased significantly during storage at 30 °C (Kapcum & Uriyapongson, 2018). The decrease in the content of bioactive phytochemical compounds from the extract can cause a loss of pharmacological activity (Postružnik et al., 2024). Therefore, it is necessary to develop plant extracts to increase the stability of their phytochemical compounds so that handling during storage and formulation becomes easier.

One of the techniques known to increase the stability of phytochemical content in plant extracts is the formation of solid dispersions (Saidan et al., 2012). Solid dispersion is the dispersion of one or more active drug ingredients in a carrier material, generally a polymer (Nair et al., 2020). The solid dispersion technique can increase the stability of active drug ingredients through physical and chemical inhibition mechanisms against the degradation process, resulting in a more stable structure (Yu et al., 2022). Solid dispersion techniques have been shown to stabilize the phytochemical content of various plant extracts (Chao et al., 2017; Chen et al., 2020; Saidan et al., 2020).

Various polymers are used as carriers in solid dispersions, one of which is polyvinylpyrrolidone (PVP) (Dudhat et al., 2023; Yu et al., 2017; Yu et al., 2022). PVP is commonly employed as a hydrophilic carrier in solid dispersion systems. Its popularity stems from properties such as a high molecular weight and a relatively low melting point. PVP also dissolves readily in water, enhancing its effectiveness in drug delivery. Moreover, it is affordable and highly biocompatible, making it suitable for pharmaceutical applications. PVP in a solid dispersion system can produce a solid solution through complexation with other components so that precipitation does not occur (Pironi et al., 2023). In addition, PVP is known to form strong hydrogen bonds with active ingredients to increase the physical stability of solid dispersion components (Yu et al., 2022). Several studies also mention that the use of PVP as a carrier in solid dispersions can increase the stability of phytochemical compounds in various extracts (Saidan et al., 2020; Jin et al., 2021; Dudhat et al., 2023; Agustina & Setyaningsih, 2023). PVP increases the stability of active ingredient molecules, among others, by increasing viscosity, generating steric barriers, and forming hydrogen bond interactions between molecules (Luo et al., 2021). PVP is known to have higher dispersibility and hydrogen bond interactions than hydroxypropyl methylcellulose and polyethylene glycol (Zhang et al., 2022). In addition, an important advantage of using PVP as a carrier is that it can also increase the solubility and dissolution rate of dispersed active ingredients, so that their bioavailability also increases (Rusdin et al., 2024).

The purpose of this study was to prepare a solid dispersion of *S. androgynus* leaf extract to increase the stability of the phytochemical content of the extract. The carrier used is a combination of PVP K30 (average MW 40,000 daltons) and PVP K90 (average MW 360,000 daltons) to produce a homogeneous solid dispersion and more intensive hydrogen bond interactions between components, resulting in a continuous barrier that can stabilize the phytochemical content of *S. androgynus* leaf extract. Previous studies have not been explored using a combined PVP K30 and PVP K90 carrier to form solid dispersions of *S. androgynu*s leaf extract. Thus, the novelty of this research lies in enhancing the stability and solid-state properties of the extract through the development of solid dispersions utilizing this carrier combination.

2. Methods

2.1. Materials and Instruments

The materials used were dry powder of *S. androgynus* leaf (UPT Materia Medica, Malang), PVP K30 (Sigma-Aldrich), PVP K90 (Sigma-Aldrich), quercetin (Sigma-Aldrich), sodium acetate, 70% ethanol (CV. Makmur Sejati), 96% ethanol (CV. Makmur Sejati), distilled water (CV. Makmur Sejati), and filter paper (CV. Makmur Sejati). The main instruments used were a rotary evaporator (Heidolph Laborota 4000), drying oven (Memmert UN 55), powder X-ray diffractometer (Panalytical X'Pert Pro), differential scanning calorimeter (Thermo plus EVO2), scanning electron microscope (Hitachi TM3000), ion sputter coater (Hitachi E-1045), and UV-Vis spectrophotometer (Hitachi U-1800).

2.2. Extraction of *S. androgynus* leaf powder

The extraction process was carried out using a method referring to Hikmawanti et al. (2021) with slight modifications. The dry powder of *S. androgynus* leaf was placed in a glass container. 70% ethanol was added to the dry powder at a ratio of 5:1 (w/v), and the container was sealed tightly. It was then left to macerate for 24 hours at room temperature. Afterward, the mixture was filtered through filter paper using a Buchner funnel, and the residue was subjected to two additional maceration cycles. The solvent from the macerate was evaporated with a rotary evaporator (Heidolph Laborota 4000) at a temperature of 45°C until a thick extract was obtained, and it was then continued using a drying oven (Memmert UN 55) at a temperature of 45°C for 3 days.

2.3. Preparation of Solid Dispersion

S. androgynus leaf extract and carrier (PVP K30 and PVP K90) with specific ratios (Table 1) were each dissolved with 96% ethanol in a glass beaker. The extract solution and carrier were mixed using a magnetic stirrer (300 rpm, 7 minutes). The mixture of extract and carrier was evaporated at a temperature of 50°C for 24 hours to produce a dry solid. The solid dispersion of *S. androgynus* leaf extract was then reduced using a mortar to produce a solid dispersion powder.

Table 1 Composition of solid dispersion of *S. androgynus* leaf extract

Formula	*S. androgynus* leaf extract	PVP K30	PVP K90
F1	1	3	0
F2	1	1.5	1.5
F3	1	1	2

PVP= Polyvinylpyrrolidone

2.4. Characterization of Solid Dispersions

2.4.1. Powder X-Ray Diffraction

PXRD characterization was performed using an X-ray diffractometer (Panalytical X'Pert Pro) with a CuKα1 radiation source (λ = 1.541 Å). The sample was inserted into the cavity of the sample holder. It was carefully positioned to ensure proper placement. A spatula was then used to level the surface of the sample. A voltage of 40 kV and a current of 30 mA were applied during the test. Scanning was performed at 10 degrees per minute, and data were collected at 2θ ranging from 5 to 50° (Wicaksono et al., 2021).

2.4.2. Differential Scanning Calorimetry

Samples of around 2 mg were placed in aluminum hermetic sample pans and sealed tightly. The pans were placed into the sample chamber of the DSC equipment (Thermo plus EVO2) and then tested with a heating rate of 10 °C per minute at 30-350 °C in dry air atmospheric conditions (Wicaksono et al., 2021).

2.4.3. Scanning Electronic Microscopy

SEM characterization was carried out using a Hitachi TM3000 equipped with an ion sputter (Hitachi E-1045), following the procedure of Wicaksono et al. (2021) with slight modifications. The samples were spread over the tape on a stainless-steel stub and then coated with platinum using a sputter coater ion at 40 mA for 20 seconds. The sample particles were observed at a voltage of 30 kV and a current of 10 mA with appropriate magnification.

2.5. Stability Test

A sample was placed in a vial and incubated at 60ºC. The total flavonoid content was evaluated on days 1 and 30 using a colorimetric assay, with quercetin as the standard. To prepare the test solution, 100 mg of the solid dispersion or 25 mg of the pure *S. androgynus* leaf extract was dissolved in 10 mL of 96% ethanol. To this solution, 0.5 mL was combined with 0.1 mL of 1 M sodium acetate, 0.1 mL of a 10% aluminum chloride solution, 1.5 mL of ethanol, and 2.8 mL of distilled water to achieve a total volume of 5 mL. This mixture was allowed to stand at room temperature for 30 minutes. Absorbance was then measured at 428 nm using a UV-Vis spectrophotometer (Hitachi U-1800). Flavonoid levels were calculated by comparing the absorbance values to a quercetin calibration curve, and results were reported as milligrams of quercetin equivalent per gram of sample (mg QE/g). The percentage of total flavonoid content retention after 30 days was calculated using the formula: (total flavonoid content on day 30 / total flavonoid content on day 1) × 100%. All tests were triplicate (Vongsak et al., 2013; Saidan et al., 2020; Hikmawanti et al., 2021).

2.6. Statistical Analysis

A statistical analysis was performed to determine differences in total flavonoid content between data groups using a one-way analysis of variance (ANOVA), followed by Bonferroni's post hoc test. Differences between data groups were considered statistically significant if the p-value was <0.05.

3. Results and Discussion

3.1. Results

3.1.1. Extract and Solid Dispersion of S. androgynus leaf extract

The results of *S. androgynus* leaf extract using the maceration method with 70% ethanol solvent are shown in Figure 1a. *S. androgynus* leaf extract is semi-solid, blackish-green, and has a distinctive odor. The results of the extract have a yield value of 17.28% (w/w). Solid dispersions of *S. androgynus* leaf extract with PVP K30 and PVP K90 carriers are shown in Figures 1b-d. Solid dispersions F1, F2, and F3 showed brownish-green powder.

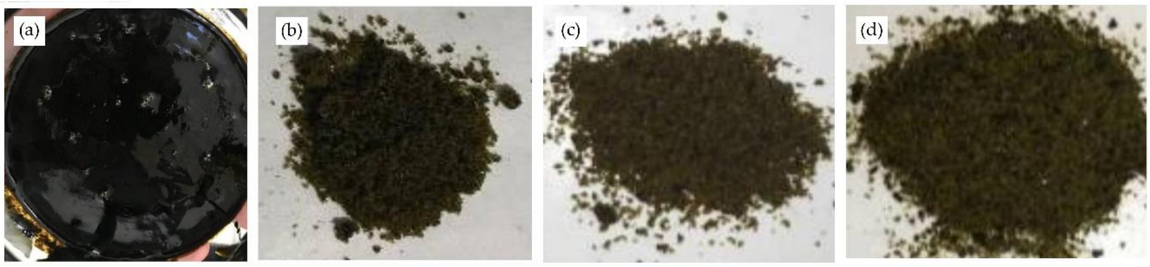

Figure 1 a) *S. androgynus* leaf extract, b) solid dispersion F1, c) solid dispersion F2 and d) solid dispersion F3. (F1= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:3:0); F2= *S. androgynus* leaf extract-PVP K30-PVPK90 (1:1.5:1.5); F3= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:1:2))

3.1.2. PXRD Diffractogram

The PXRD diffractogram of the solid dispersion is shown in Figure 2. The diffractogram of *S. androgynus* leaf extract solid dispersion (F1, F2, and F3) did not show any sharp diffraction peaks, but there were two halo patterns with broad peaks, namely at 2θ around 10 and 21°.

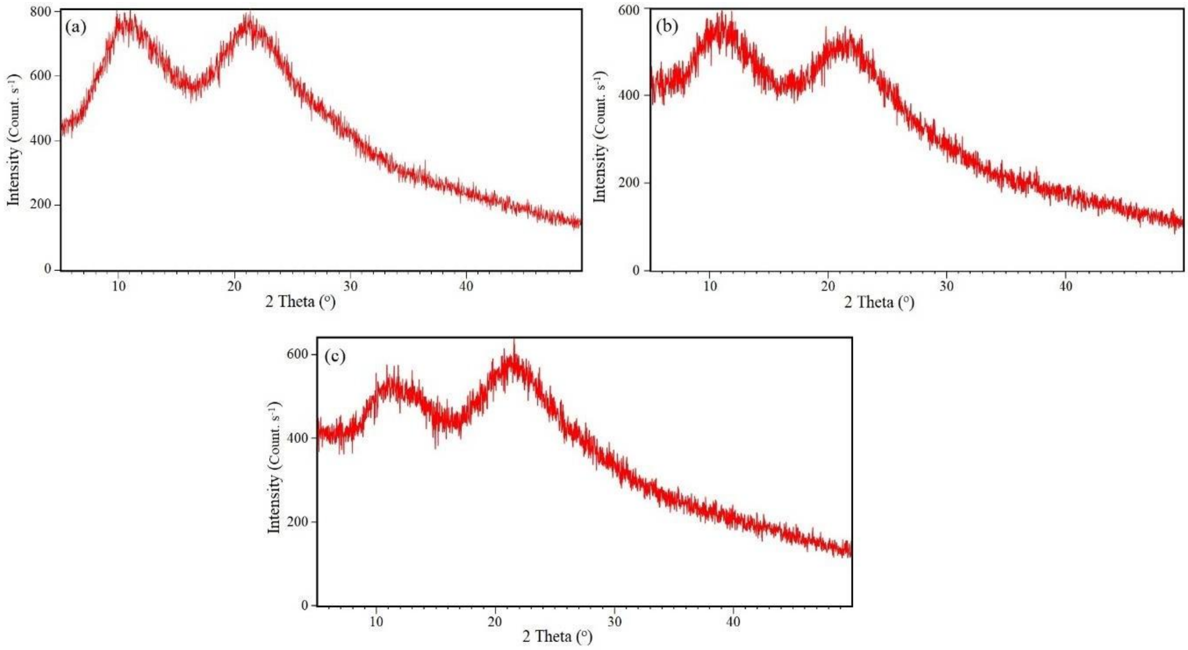

Figure 2 PXRD diffractograms of a) solid dispersion F1, b) solid dispersion F2, and c) solid dispersion F3. (F1= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:3:0); F2= *S. androgynus* leaf extract-PVP K30-PVPK90 (1:1.5:1.5); F3= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:1:2))

3.1.3. DSC Thermogram

The DSC thermogram of the solid dispersion is shown in Figure 3. DSC thermograms of solid dispersions F1, F2, and F3 do not have sharp endothermic peaks until 150 °C. Solid dispersion F1 showed a broad endothermic peak at around 80 - 140 °C. The glass transition temperature peak in the thermograms of solid dispersions F1, F2, and F3 appeared at around 160- 170 °C (marked with a black arrow in the figure). In the thermograms of solid dispersions, F1, F2, and F3 showed sharp endothermic peaks at around 175.3 - 180.5 °C.

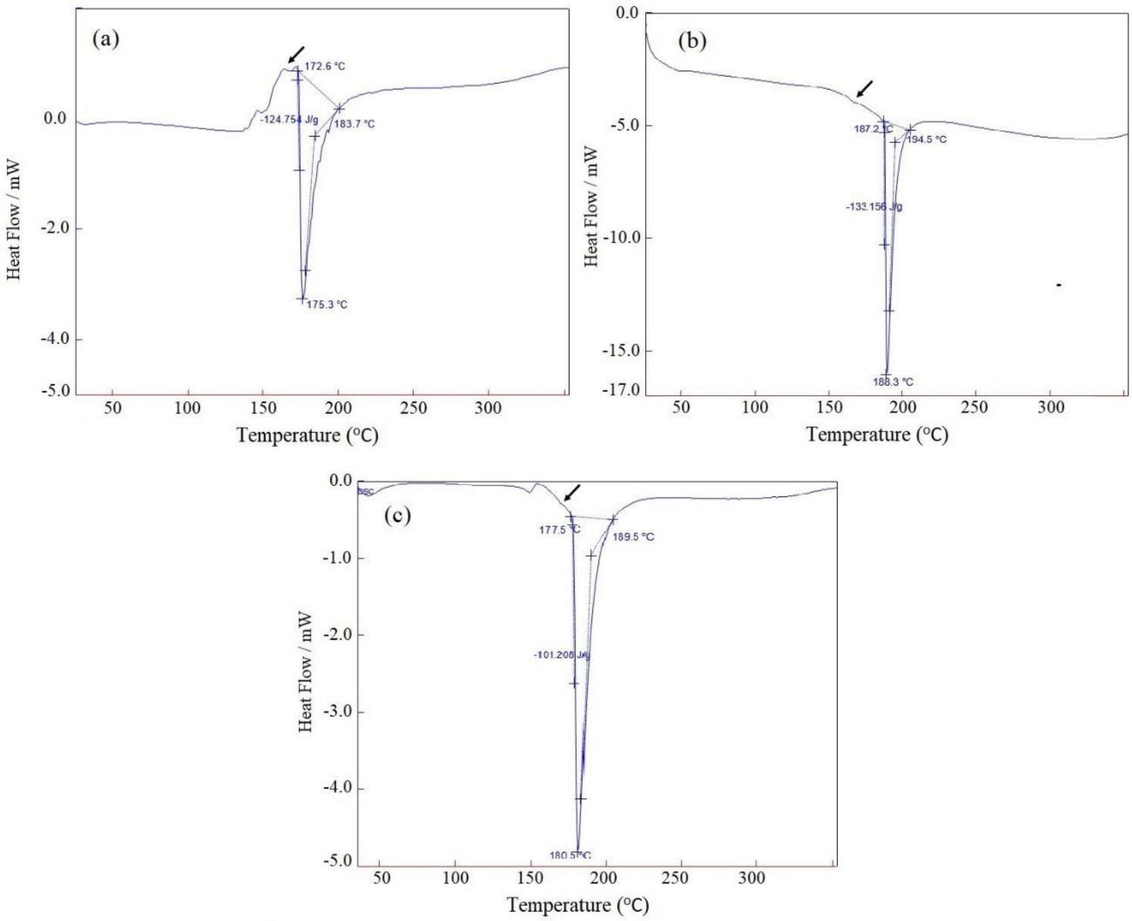

Figure 3 DSC thermograms of a) solid dispersion F1, b) solid dispersion F2, and c) solid dispersion F3 (F1= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:3:0); F2= *S. androgynus* leaf extract-PVP K30-PVPK90 (1:1.5:1.5); F3= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:1:2))

3.1.4. SEM Micrograph

SEM micrograph of solid dispersion of *S. androgynus* leaf extract is shown in Figure 4. Micrographs of solid dispersions F1, F2, and F3 showed irregular particle shapes with varying rough and smooth surface topography. Solid dispersion particles of *S. androgynus* leaf extract F1, F2, and F3 were almost the same size, namely a diameter of around 0.1 - 0.5 mm.

3.1.5. Stability of Flavonoids in Solid Dispersion

The total flavonoid content in pure leaf extracts and *S. androgynus* leaf extracts solid dispersions at storage conditions at a temperature of 60 °C is shown in Table 2. The pure extract of *S. androgynus* leaf on day 1 showed a total flavonoid content of 26.31 ± 2.01 mg QE/g sample, while the solid dispersions F1, F2, and F3 on day 1 showed total flavonoid contents of 5.10 ± 0.15, 5.28 ± 0.11, and 5.56 ± 0.25 mg QE/g sample, respectively. After storage for 30 days at a temperature of 60ºC, the total flavonoid content in the pure extract was 13.65 ± 1.12 mg QE/g sample, while the solid dispersions F1, F2, and F3, stored under the same conditions for 30 days, had total flavonoid contents of 4.84 ± 0.15; 5.04 ± 0.53; and 5.29 ± 0.43 mg QE/g sample, respectively.

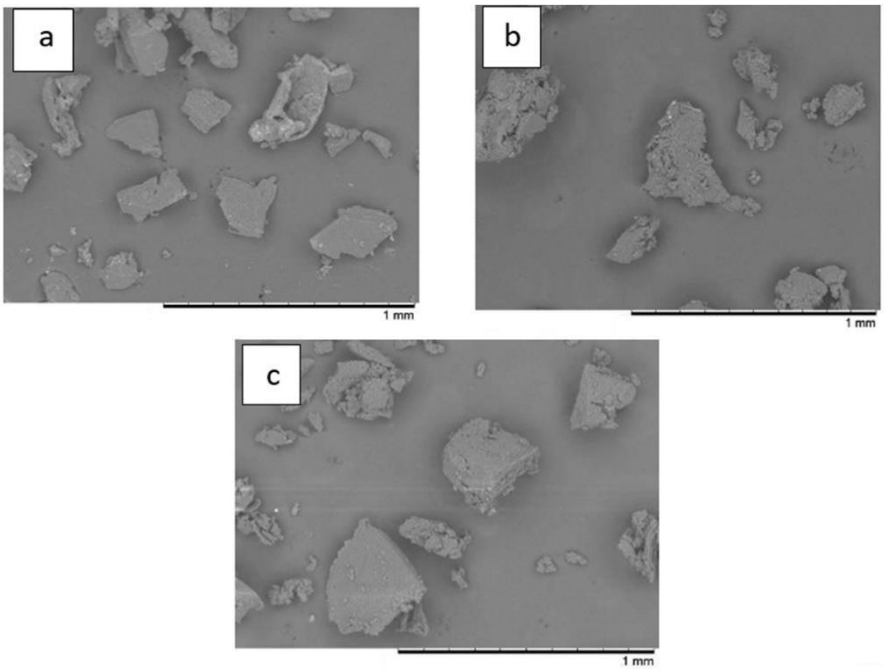

Figure 4
Micrographs of a) solid dispersion F1, b) solid dispersion F2, and c) solid dispersion F3 (100x) (F1= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:3:0); F2= *S. androgynus* leaf extract-PVP K30-PVPK90 (1:1.5:1.5); F3= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:1:2))

Table 2 Total flavonoid content in pure extract and solid dispersion

Sample	Day 1		Day 30		
	TFC (mg QE/g sample)	TFC remaining (%)	TFC (mg QE/g sample)	TFC remaining (%)	Decrease TFC (%)
Pure extract	26.31 ± 2.01	100.00	13.65 ± 1.12	51.88	48.12
F1	5.10 ± 0.15	100.00	4.84 ± 0.15	94.90	5.10
F2	5.28 ± 0.11	100.00	5.04 ± 0.53	95.45	4.55
F3	5.56 ± 0.25	100.00	5.29 ± 0.43	95.14	4.86

TFC = Total flavonoid content, data are presented as mean ± SD (n =3), (F1= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:3:0); F2= *S. androgynus* leaf extract-PVP K30-PVPK90 (1:1.5:1.5); F3= *S. androgynus* leaf extract-PVP K30-PVP K90 (1:1:2))

3.2. Discussion

S. androgynus leaf powder was extracted using the maceration technique with 70% ethanol solvent, while the solid dispersion was prepared using a combination of PVP K30 and PVP K90 carriers. The result of *S. androgynus* leaf extract has a semi-solid consistency and was blackish-green in color, as shown in Figure 1a. The extract yield value from *S. androgynus* leaf powder extraction was 17.28% (w/w). The extract yield is influenced by, among others, the raw materials, the type of extraction solvent, and the extraction method. Using dry raw materials generally produces a higher extract yield than wet raw materials. When using a mixture of ethanol and water as a solvent for the extraction process, 70% ethanol extracts more total flavonoids than 96% ethanol (Hikmawanti et al., 2021).

The solid dispersion of *S. androgynus* leaf extract with PVP K30 and PVP K90 carriers appeared as a brownish-green powder (Figure 1b-d). The ratio of *S. androgynus* leaf extract to the carrier (PVP K30 and PVP K90) was 1:3, which can produce a dry powder of solid dispersion. Solid dispersions showed as powders with irregularly shaped particles, having smooth or rough surface topography. The solid dispersion particles have a diameter range of around 0.1 - 0.5 mm. The morphology of solid dispersion particles affects the physicochemical properties such as flow properties, dissolution, and compressibility. Generally, particles with a spherical shape have good flow properties, while solid dispersion powders with smaller particle sizes have faster dissolution rates (Ekdahl et al., 2019; Csicsák et al., 2023).

The results of PXRD characterization showed that the diffractogram of the solid dispersion powder has two halo patterns without sharp diffraction peaks, as shown in Figure 2. The diffractogram indicated that the solid dispersions F1, F2, and F3 were amorphous solids (Jin et al., 2021; Budiman et al., 2023). Plant extracts contain multicomponent phytochemicals, generally amorphous solids (Rani et al., 2024; Tafu & Jideani, 20). As solid dispersion carriers, PVP K30 and PVP K90 are also amorphous solids (Khuanekkaphan et al., 2024). PVP K30 and PVP K90 formed hydrogen bond interactions with phytochemical compounds in the extract, which can inhibit recrystallization, thereby increasing the physical stability of the dispersion system. Amorphous solid dispersions with hydrophilic polymer-carriers also improve the solubility properties of poorly soluble components in the extract, thereby increasing their bioavailability (Rusdin et al., 2024).

DSC thermograms of solid dispersions do not have sharp endothermic peaks up to 150 °C (Figure 3). Solid dispersion F1 showed a very broad endothermic peak at around 80 - 140 °C, which is attributed to the evaporated water from the solid dispersion. The water content in the F1 solid dispersion is estimated because the solid dispersion carrier was only PVP K30, which can absorb more moisture. In the F2 and F3 solid dispersion thermograms, there were no endothermic peaks from water evaporation, indicating that the combination of PVP K90 as a carrier can reduce the hygroscopicity of the solid dispersion. The peak of the glass transition temperature on the solid dispersion thermogram appeared at a temperature of around 160–170°C, associated with the amorphous solid of the solid dispersion, which has also been confirmed in PXRD testing (Kallakunta et al., 2019). The thermogram of solid dispersion F1 displayed a distinct endothermic peak at approximately 175.3°C, onset at 172.6°C, and end set at 183.7°C, with a fusion enthalpy ($\triangle$H) of 124.754 J/g. Likewise, solid dispersion F2 exhibited a prominent endothermic peak around 188.3°C, starting at 187.2°C and ending at 194.4°C, accompanied by a fusion enthalpy ($\triangle$H) of 133.156 J/g. For solid dispersion F3, a sharp endothermic peak is observed at 180.5°C, with an onset at 177.5°C, an end set at 189.5°C, and a fusion enthalpy ($\triangle$H) of 101.208 J/g. The appearance of the endothermic peak in the solid dispersion thermograms (ranging from 175.3 to 188.3 °C) was thought to be due to the thermal degradation of various secondary metabolites, especially phenolic compounds present in *S. androgynus* leaf extract (Tafu & Jideani, 2021). Combining PVP K30 with PVP K90 as a carrier increased the decomposition temperature of solid dispersions compared to solid dispersions with only PVP K30 as a carrier. The increase in the decomposition temperature was thought to be because the combination of PVP K30 and PVP K90 can form stronger intermolecular interactions and coat more intensively than the single carrier (PVP K30), so that the thermal stability of the phytochemical content in the extract increases (Budiman et al., 2023; Yu et al., 2022).

In the stability test, the pure extract of *S. androgynus* leaf on day 1 showed a total flavonoid content of 26.31 ± 2.01 mg QE/g sample. The total flavonoid content in *S. androgynus* leaf extract is influenced by, among others, the raw material, type of extraction solvent, and extraction method (Hikmawanti et al., 2021). The F1, F2, and F3 solid dispersions on day 1 showed total flavonoid contents of 5.10 ± 0.15, 5.28 ± 0.11, and 5.56 ± 0.25 mg QE/g sample, respectively (Table 2), which did not show significant differences ($p>0.05$). Solid dispersions F1, F2, and F3 used a ratio of carrier and extract (3:1) so that the total flavonoid content (mg QE/g sample) was about a quarter of the total flavonoid content in the pure extract.

After 30 days of storage at 60°C, the total flavonoid content in the pure extract was 13.65±1.12 mg QE/g sample, which means that the total flavonoid content remaining was 51.88% or a decrease of 48.12% compared to the initial content (day 1). These results indicated that the total flavonoid content in the pure extract has been reduced by almost half. Flavonoid compounds can undergo degradation to produce simpler phenolic acids, whereby the degradation is influenced by light, temperature, pH, and oxygen levels (Sankaranarayanan et al., 2019). Meanwhile, in solid dispersions F1, F2, and F3, after being stored at 60°C for 30 days, the total flavonoid content was 4.84 ± 0.15, 5.04 ± 0.53, and 5.29 ± 0.43, respectively, where there was no significant difference between formulas ($p>0.05$). It can be concluded that the difference in composition of PVP K30 and PVP K90 as carriers in solid dispersions does not affect the total flavonoid content in solid dispersions after being stored at 60°C for 30 days.

The results showed that the total flavonoid content in solid dispersions F1, F2, and F3 after storage at 60°C decreased by only 4.55-5.10%. These results indicated that forming solid dispersion with PVP K30 and PVP K90 carriers can inhibit the degradation of total flavonoid content in *S. androgynus* leaf extract compared to pure extract, from 48.12% to only 4.55-5.10%. The inhibition of total flavonoid degradation in solid dispersions is thought to be due to PVP K30 and PVP K90 forming hydrogen bonds with phytochemical compounds in the extract, resulting in a homogeneous matrix. The phytochemical compounds of the extract in the solid dispersion matrix were encapsulated by the carrier (PVP K30 and PVP K90), thereby inhibiting degradation reactions caused by environmental factors (temperature, oxygen), thus enhancing their stability (Lim et al., 2021).

4. Conclusion

The solid dispersion of *S. androgynus* leaf extract formulated with PVP K30 and PVP K90 as carriers via the solvent evaporation method resulted in an amorphous solid form. Thermal analysis indicated that the phytochemical constituents within the solid dispersion showed degradation at the temperature range of 175.3–188.3°C. Compared to the pure extract, the flavonoid compounds embedded in the solid dispersion exhibited enhanced thermal stability and degraded more slowly. These findings suggested that forming a solid dispersion with PVP K30 and PVP K90 as carriers improved the stability of the phytochemicals in *S. androgynus* leaf extract.

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