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Integrity of *Annona muricata* L. leaves extract tablets with crospovidone

Fajar Handayani, Devita Kurniasari, Oktavia Indrati, Aris Perdana Kusuma*

Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia
*Corresponding author: arisperdana@uii.ac.id

Abstract
Background: *Annona muricata* L. (*A. muricata*) leaf contains several active compounds, including flavonoids, which are known to have antioxidant properties. People only use *A. muricata* leaves as antioxidants by boiling them in water. Therefore, the development of tablet potential is necessary to enhance user comfort and storage stability.
Objective: The aim of this research was to determine the disintegration time of *A. muricata* leaf extract tablets with varying levels of the disintegrating agent crospovidone and to determine the best disintegrating level according to the results of evaluating the physical properties of the tablets.
Methods: Tablets are made using the wet granulation method, incorporating a composition of 2-5% crospovidone. The resulting granules are tested for water content, flow time, angle of repose, and tapping. The resulting tablets were tested for hardness, friability, and disintegration time.
Results: The test results show that crospovidone and lactose can produce excellent *A. muricata* leaf extract tablets.
Conclusion: Crospovidone 3.5% produces optimum *A. muricata* leaf extract tablets with a friability of 0.36% and a disintegration time of 7.82 minutes.
Keywords: *Annona muricata* L. leaf, crospovidone, disintegrant, tablet

1. Introduction

Indonesia is home to numerous plants with medicinal properties that can be explored as traditional medicine ingredients. One such example is *Annona muricata* L. (*A. muricata*), commonly known as soursop or *sirsak*. The leaf of this plant has been traditionally used by local communities for the prevention and treatment of various diseases. Phytochemical analysis has revealed that ethanol extracts (70%) from *A. muricata* leaf contain a range of bioactive compounds, including alkaloids, flavonoids, saponins, tannins, quinone steroids, essential oils, and coumarins. These compounds exhibit antioxidant potential, which may contribute to the plant's therapeutic effects.

In vitro studies have demonstrated that *A. muricata* leaf possesses beneficial effects on pancreatic tissue function by enhancing the activity of antioxidant enzymes and insulin hormone levels. Additionally, the leaf contains acetogenin compounds with cytotoxic properties against cancer cells, suggesting a role in immune system protection and prevention of life-threatening infections (Adewole & Caxton-Martins, 2009).

In addition to containing acetogenin compounds, *A. muricata* leaf also possesses flavonoid components with potential antioxidant and therapeutic properties. Antioxidants are molecules that function by inhibiting free radical reactions in the body, protecting cells from toxic effects, and contributing to disease prevention. Traditional herbal medicines like those derived from *A. muricata* leaf tend to have fewer side effects compared to synthetic chemical-based medications. The *A. muricata* leaf extract has been shown to possess

stronger antioxidant activity than other Annona species. The various chemical compounds present in the leaf, including sesquiterpenoids, phenolic acids, and 2,3-dihydrobenzofurans, exhibit good antioxidant properties (Badmus *et al*., 2020).

A. muricata leaf is typically consumed by boiling them with water; therefore, innovative approaches are needed to facilitate their use. The leaf can be formulated into pharmaceutical preparations like tablets to enhance convenience and stability in usage. Tablet formulation requires various additives such as fillers, binders, lubricants, and disintegrants. Different formulas and processes can be combined to achieve desirable tablet properties.

One critical parameter for the success of a tablet formula is its dissolution time in the gastrointestinal tract. The addition of disintegrants like crospovidone (CPV) was performed to facilitate this process. CPV has high capillary action, allowing water to quickly enter the pores of the tablet and weaken interparticulate bonds, causing the tablet to break apart.

Prior studies have investigated and formulated tablets from *A. muricata* leaf extracts using various additives such as primojel, CMC Na - sodium starch glycolate (SSG), povidone K30 (Pov30) - croscarmellose sodium (CCS) (Endriyatno, 2018). Some studies have even specifically used the Pov30 – CPV combination. However, some of these studies did not yield tablets with a good balance between friability and dissolution time.

Therefore, this study aimed to select suitable materials supported by an appropriate compaction process. The Pov30 - CPV combination was used and re-optimized in this study. This combination theoretically will balance the tablet's integrity or strength against its dissolution rate in the gastrointestinal tract. Process parameters such as compaction were also adjusted to achieve physical properties that meet requirements.

This study is expected to provide a reference for the pharmaceutical industry in formulating herbal products, particularly *A. muricata* leaf extracts. Different formulations, even those with small differences in materials and processes, will result in different products. Therefore, this study can be used as a basis for re-optimizing or confirming previous studies' findings.

2. Method

2.1. Material

The main material used was a dried extract of *A. muricata* (Borobudur Natural Herbal Industry; ethanol extract with maltodextrin drying 10:1). The additives used were

Pov30 and CPV (Hangzhou Nanhang), lactose (Fontera), as well as magnesium stearate (Peter Greven).

2.2. Method

Tablet formulations were prepared by varying the concentration of CPV (2-5%) as shown in **Table 1**. Wet granulation was employed for tablet production. The binder was prepared by dissolving 2% Pov30 in ethanol. A mixture of dried extract, lactose, and half of the CPV was homogenized and then mixed with the binder. The wet granules were sieved, dried, re-sieved, and subsequently blended with magnesium stearate and the remaining CPV. The resulting granule mixture was subjected to evaluation. Subsequently, the granules were compressed into tablets, which were also subjected to testing (**Figure 1**).

Two analytical approaches were employed: (1) the direct method, where individual formulations were tested and compared based on physical properties, and (2) the design of experiments (DoE) approach, where a systematic mixture design was applied using Design Expert software to evaluate the effects of CPV concentration on tablet characteristics. In the direct method, each formulation was evaluated based on granule and tablet test results, with the best-performing formula selected according to critical quality attributes. The DoE approach, in contrast, utilized statistical modeling to predict the optimal composition rather than relying solely on empirical selection. This method enabled the identification of trends in formulation performance and provided a data-driven approach to optimizing tablet properties.

2.2.1. Granule evaluation

The granule flow test was conducted after mixing, prior to compression into tablets. The powder flow test was performed using a funnel and tapping. The flow rate was determined by pouring 100 g of powder through the funnel and recording the time taken for it to pass through. The flowed powder was then measured for its height and diameter to obtain an angle of repose value (Awaluddin *et al*., 2017; USP, 2016).

Table 1. Formula of *A. muricata* leaf extract tablets

Material (mg)	FI	FII	FIII
A. muricata Leaf Extract	100 mg	100 mg	100 mg
Lactose	370 mg	362.5 mg	355 mg
CPV	10 mg	17.5 mg	25 mg
Pov30 2%	10 mg	10 mg	10 mg
Mg stearate 2%	10 mg	10 mg	10 mg

Figure 1. Flowchart of the preparation and testing of *A. muricata* leaf extract tablets

The tapping test was conducted on 100 mL of powder, which was tapped a total of 100 times. This process continued until a constant volume was achieved. The tapping index was determined based on the calculation between the final and initial volumes (100 mL) (USP, 2016).

2.2.2. Tablet evaluation

The tablet testing was conducted on tablets after compression, which included tests for weight, hardness, disintegration, and friability (USP, 2016). The weight test was performed by weighing ten tablets on an analytical balance to determine any variation in weight between tablets. The hardness of the tablets was evaluated using a hardness testing device. The hardness value was determined as the mean of 10 measurements.

The next test was conducted by placing ten tablets in a friability tester. The tablet was rotated on this device for four minutes at a speed of 25 RPM. Subsequently, the disintegration test was performed with six samples of each formula, which were placed in an aqueous medium. The results of the test were determined based on the duration until the tablets had completely disintegrated and no granule residue remained on the mesh surface (Martinello *et al*., 2006).

3. Results and discussion

3.1. Granule evaluation

The granule evaluation was conducted on dried granules to determine whether their characteristics meet the requirements for good tablet quality, as the properties of the granules will affect the quality of the tablets (**Figure 2**). The results of the granule evaluation can be seen in **Table 2**.

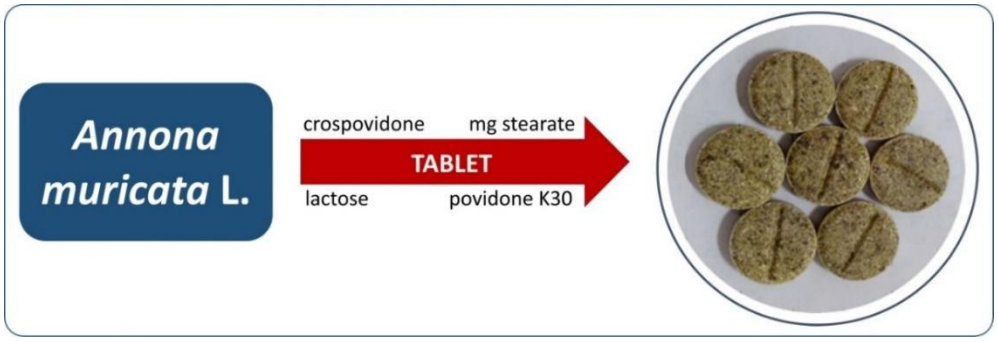

Figure 2. Illustration of tablet formulation
Note: The image used is Tablet F2. Other formulas have similar-looking tablets.

Table 2. Granule properties of *A. muricata* leaf extract tablets

Parameter	F1	F2	F3
Moisture content (%)	2.12±0.23	1.48±0.29	1.81±0.46
Flow speed (g/s)	14.23±0.05	15.02±0.18	14.39±0.06
Angle of repose (°)	30.53±1.11	30.52±1.11	30.67±0.96
Tapping index (%)	20.00±0.81	22.66±1.52	23.00±1.00

3.1.1. Moisture content

The moisture content test on granules was conducted using a moisture balance at 105°C. The level of moisture will affect the manufacturing and storage processes of the dosage form. Factors that influence moisture content include room humidity, drying of granules, and physical properties of the extract itself. This test is very important because it relates to flowability, compaction process, compactibility, and stability. In general, the moisture content of granules ranges from 2-5%. The results show that all three formulas have achieved a suitable moisture level, ranging from 1.48 to 2.12%. The heating performed for 24 hours in an oven played a significant role in achieving this result. Optimal moisture levels will affect the compaction process of tablets. Granules that are too moist will make tablets very hard and slow down their disintegration time. On the other hand, extremely dry granules will make tablets prone to being fragile (Gabbott *et al*., 2016; USP, 2016).

3.1.2. Flow speed

The United States Pharmacopeia (USP) recommends evaluating granule flow rate as a parameter to assess the smoothness of granules flowing into tablet compression machines. The quality of this flow is influenced by several factors. including particle size, shape, and density, as well as moisture content. Poor granule flow can result in inconsistent tablet weights, compromising the uniform distribution of active ingredients (Goh *et al*., 2017).

The test results show that all formulas have a good flow rate, namely > 10 g/second. The binder Pov30 can help in maintaining cohesion between particles so that powder from different materials can remain united as one compact granule. Since the granules are

physically larger than powders, their flow rates will be even better (Lamešić *et al*., 2017; USP, 2016).

3.1.3. Angle of repose

The angle of repose is commonly utilized to determine granule flow characteristics. The angle of repose refers to the maximum angle formed between the surface of a material and a flat plane when that material is poured from a funnel. The angle of repose can provide information about the smoothness of flow and the ability of a material to flow. The smaller the angle of repose, the better the flow properties of the material are. Test results show that all formulas have good angles of repose because they are <35°. The differences in variations among the three formulas do not result in significant differences in the angle of repose values. Instead, the testing results indicate that any formula used in this study will produce powders with good flow properties (Kaleemullah *et al*., 2017; USP, 2016).

3.1.4. Tapping evaluation

The tapping test is an indirect method for evaluating granule flow properties by assessing the material's ability to settle after repeated vibrations. The test is quantified using the T% index (%), where lower values indicate better settling and improved flowability, typically associated with fewer fines capable of filling interparticle spaces. The T% index is largely influenced by the granule mixture's ability to fill voids and achieve tighter packing during vibration. Flowability is determined by multiple factors. including particle shape, brittleness, and size distribution. A T% index of less than 20% is generally indicative of good flow properties, with smaller T% values reflecting superior flowability (Alkrad *et al*., 2017; USP, 2016).

The calculated values from Formulas I, II, and III yielded results of 20%, 22.66%, and 23% respectively. Based on these values, it can be concluded that the granule exhibits moderate flow properties due to its T-index falling within the range of 20-23%. This suggests that the granules have an irregular shape, a non-uniform size distribution, were exposed to air for too long, and experienced significant volume reduction, ultimately resulting in a high T-index value (Alkrad *et al*., 2017; USP, 2016).

3.2. Tablet evaluation

3.2.1. Weight variation

The weight variation test, as described in **Table 3**, is a method for determining the level of weight variability within a batch production. This testing ensures that each tablet in a single batch has a uniform or only slightly deviating weight from the average weight. Insufficient weight can result in a dose lower than specified, leading to reduced efficacy.

Conversely, excessive weight may cause an overdose of active ingredients, increasing the risk of adverse effects and exceeding specifications (Kaleemullah *et al*., 2017; USP, 2016).

Table 3. Evaluation results of the physical properties of *A. muricata* leaf extract tablets

Evaluation	F1	F2	F3
CV of weight (%)	1.05	2.18	1.98
Hardness (kgf)	5.37±0.42	5.31±0.30	5.40±0.68
Friability (%)	0.16±0.22	0.36±0.30	0.55±0.70
Disintegration time (min)	13.98±3.77	7.82±0.10	5.68±0.07

3.2.2. Tablet hardness

The hardness test is conducted to determine the level of firmness or strength of a tablet. This testing ensures that the produced tablets have an appropriate hardness, preventing them from breaking easily during production, distribution, and storage processes. Additionally, it guarantees that the tablets can be quickly disintegrated with ease in the body upon consumption (Martinello *et al*., 2006; USP, 2016).

3.2.3. Tablet friability

The friability test is conducted to determine a tablet's resistance to impact and vibration. This testing ensures that the produced tablets have sufficient mechanical strength, preventing them from breaking or becoming damaged during processes such as compression, packaging, and transportation. This test is crucial because high friability can cause damage to the shape of pharmaceutical preparations, ultimately reducing their efficacy (Alkrad *et al*., 2017; USP, 2016).

3.2.4. Disintegration test

The disintegration test assesses how rapidly a tablet breaks down into small particles and releases its active compounds within bodily fluids. This testing employs water as the medium, simulating the conditions of gastric or intestinal fluid erosion using an apparatus that moves up and down. For immediate-release tablets, it is anticipated that they will quickly disintegrate upon contact with these fluids, thereby delivering the intended therapeutic effect in a timely manner (Martinello *et al*., 2006).

In this formulation, crospovidone (CPV) as super disintegrant can absorb water and swell to push out particle matrix of tablets. This will accelerate tablet disintegration when it comes into contact with gastrointestinal fluids. The longest disintegration time was achieved by F1 with the lowest grinding material content, while the fastest was F3 with the highest CPV composition. All formulas showed good results for disintegration times. Therefore, at least, these tablets can quickly disintegrate within 15 minutes when in contact with gastrointestinal fluids. However, selecting the best formula cannot solely be based on the fastest disintegration time. Other parameters such as tablet friability must also be considered to determine the optimal formulation (Awaluddin *et al*., 2017; USP, 2016).

3.3. General testing and optimal formulation

The results from the direct method showed that F2 exhibited the best overall performance, with a friability of 0.36% and a disintegration time of 7.82 minutes. In contrast, F1 had lower friability but a significantly longer disintegration time, nearing 15 minutes. Meanwhile, F3 demonstrated a shorter disintegration time but higher friability. Notably, in one measurement, F3 exceeded the standard friability limit of 1%, reaching 1.35%, resulting in a high standard deviation. Based on these findings, F2 was identified as the most favorable formulation among the tested samples.

In the second approach, the design of experiments (DoE) method, an optimization simulation was performed using a mixture design in Design Expert software (**Figure 3**). The goal was to minimize both friability and disintegration time while identifying the optimal composition. The predicted optimal formulation consisted of LAK:CPV at a ratio of 363.13 mg:16.86 mg, corresponding to a CPV concentration of 3.4%. The model predicted a disintegration time of 9.51 minutes and a friability of 0.34%. While the predicted disintegration time was slightly longer than that of F2, the lower friability suggested improved mechanical integrity. This approach allowed for a systematic evaluation of formulation variables, demonstrating that statistical modeling could predict an optimized composition beyond simply selecting the best-performing tested sample.

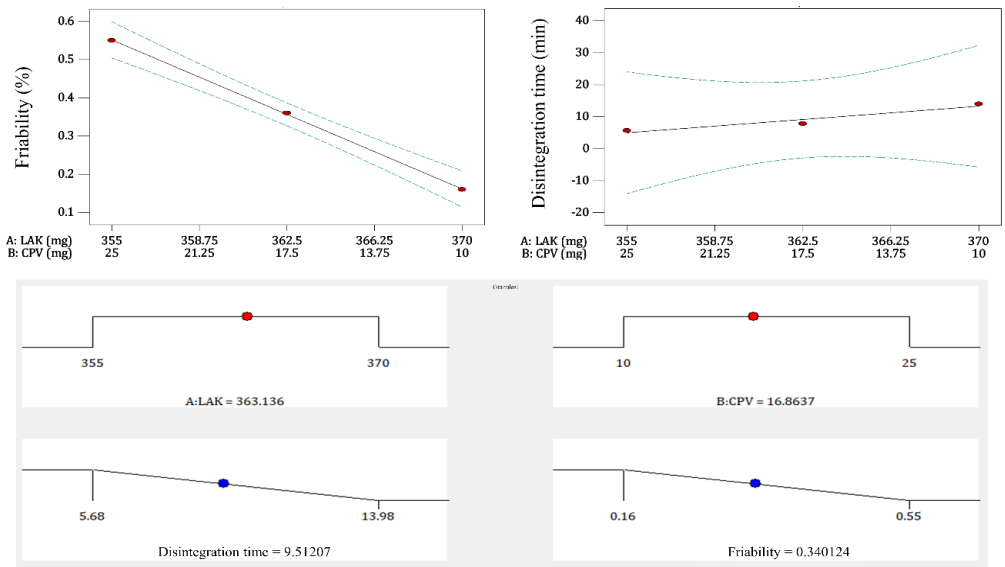

Figure 3. Formula optimization using mixture design

The variability observed in tablet friability testing across measurements is likely attributed to the mixing process. Prolonged mixing or optimizing the mixing speed may address this issue. However, it is important to note that the variations do not overlap and

still exhibit a consistent trend in friability percentages: F1 < F2 < F3. Thus, these inconsistencies do not alter the conclusions regarding tablet friability.

Another parameter to consider is compression pressure. All tablet formulations were produced under the same compression pressure, resulting in tablet hardness of approximately 5 kgf. Slightly increasing the compression force could further reduce the friability values. Nonetheless, even under the current parameters, all formulations generally meet the requirements for tablet friability testing (Alkrad *et al*., 2017).

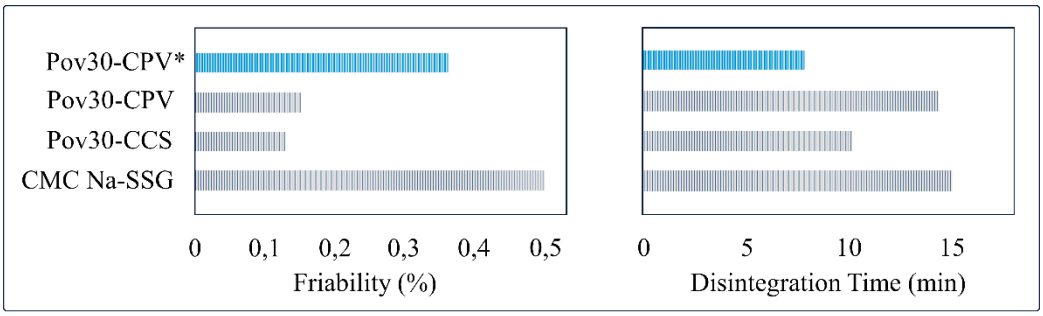

Figure 4. Comparison of *A. muricata* leaf extract tablet formulations in this study (*) with other studies using different excipients

One of the primary testing parameters for herbal tablets is disintegration time, which indicates how quickly a tablet breaks apart and releases its active ingredient upon contact with gastrointestinal fluids. F2, identified as the optimal formulation, exhibited excellent disintegration performance, with a value of under 10 minutes. Compared to formulations reported in other studies (**Figure 4**), which utilized disintegrants such as povidone K30-CPV, povidone K30-CCS, and CMC-Na – SSG, the F2 formulation demonstrated superior disintegration performance. While some of these alternative excipient systems may have resulted in lower friability, their disintegration times were generally longer. The rapid disintegration of F2 suggests that the specific ratio of Pov30 - CPV in this study provided a more efficient tablet breakdown, which is a critical factor for herbal tablet formulations (Endriyatno, 2018).

4. Conclusion

A. muricata was successfully formulated into tablets using povidone K30 as a binder and CPV as a super disintegrant. The direct method identified Formula II (containing 3.5% CPV) as the best-performing formulation, exhibiting a friability of 0.36% and a disintegration time of 7.82 minutes. Meanwhile, the design of experiments (DoE) approach predicted an optimized formulation with 3.4% CPV, yielding a friability of 0.34% and a disintegration time of 9.51 minutes. These findings demonstrate that statistical modeling

can provide an optimized formulation beyond empirical selection, balancing key tablet properties for enhanced performance.

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