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Research Paper

Tablet Formula Optimization From *Helminthostachys Zaylanica* Extract Using A *Simplex Lattice Design*

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Abstract
Helminthostachys zeylanica extract has pharmacological activities such as antioxidant, antiinflamatory, and antihyerucemia. This extract is nontoxic substance from the acute and subchronic toxicity tests. This extract has a potency to be formulated into tablet dosage forms. This study aims to optimize a tablet formula from *Helminthostachys zeylanica* extract. Disintegrant and binder concentrations were independent variables, while physical properties and dissolution time of the tablets were dependent variables. The tablet was prepared by a wet granulation method. Formula was optimized by Simplex Lattice Design. Physicochemical properties of granule, physical properties and dissolution of tablet were then analyzed with One Way ANOVA (p = 0.05). Based on granule analysis, specification of physicochemical parameters, such as hausner's ratio, compressibility index, flowability, repose angle, and water content, met standard British Pharmacopeia. In addition, the starch and PVA concentrations influenced thickness, weight variation, hardness, friability, disintegration time and dissolution of the tablets (p <0.05), except for friability (p> 0.05). Based on this study, the starch and PVA concentrations for the optimum tablet formula were 19.5% and 1.05%, respectively.

Keywords
Helmynthostachis zeylanica, Tablet, Optimization, Simplex Lattice Design

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1. INTRODUCTION

Helminthostachys zeylanica known as Tunjuk Langit (TL), has active components, such as ugonstilben A-D and flavonoids ugonin E-M (Chen et al., 2003; Fitrya, 2010; Wu et al., 2017) Pharmacological activities of the extract of TL has been reported as an antioxidant (Huang et al., 2003), anti inflammatory (Huang et al., 2017; Su et al., 2016), hepatoprotective (Suja et al., 2004), antihyperuricemia (Fitrya and Muharni, 2014) and antidiabetic (Chang et al., 2019; El Ridhasya et al., 2020). Based on a toxicity test of the extract, it was reported to be safe for consumption (Fitrya, 2017).

Nowadays, the use of herbal medicine is becoming more popular. Extract formulations into pharmaceutical dosage forms are increasingly developed for both topical and oral uses. The most popular-oral dosage is a tablet form because it is easy for consumption and is better stability (de Souza et al., 2007; Nguyen et al., 2013). Several studies on tablet formulations of the herbal extracts were reported such as tablets from *Morus alba* extract (Son et al., 2018), *Ginger dry* extract (Malek et al., 2020); *Pachyrrhizus erosus* extract (Kharisma et al.); *Curcuma longa* exctract (Ermawati et al., 2017); and *Phillanthus niruri* extract (de Souza et al., 2007).

The herbal extracts tend to be high hygroscopic because they are composed from carbohydrates as a major component. The hygroscopic properties of the extract influence the flow properties. Furthermore, these flow properties cause tablet compactibility if they are formulated to a tablet dosage form. Therefore, the determination of the type and concentration of the excipient will determine the quality of the tablets (Son et al., 2018). In the preliminary study we have prepared three tablet formulations of the TL rhizome ethanol extract using different disintegrant and binder combinations, i.e., formula A: Starch & Polyvinyl Alcohol (PVA); formula B: Avicel®PH102 and Polyvinyl Pirolidone (PVP); and formula C: sodium alginate & methylcellulose. Based on physical properties and dissolution of the tablets, formula A had the best physical properties and dissolution(Fitrya, 2016). The main function of disintegrant is contrary to binder efficiency but the disintegrant and binder are essential components which determine an ability of tablet disintegration. The stronger the binder, the more effective the disintegrant must be for the tablets to release its medicine. Disintegrant plays an important role of water absorption into the tablet matrix, so that the tablets turn into granules and subsequently become primary particles. The formation of primary

particles increases the dissolution rate and bioavailability of the drug (Desai et al., 2016; Dilebo and Gabriel, 2019). Therefore, the type and concentration of disintegrant and binder are important to ensure a good bioavailability of drug (Bhowmik et al., 2010). This study aims to determine optimum disintegrant and binder concentration in a tablet formula. Optimum concentration was determined by *Simplex Lattice Design* (SLD) using software *Design Expert*®8 (DX®8)

2. EXPERIMENTAL SECTION

2.1 Material

The active ingredient was ethanol extract of the TL rhizome. This rhizome was collected from Ogan Ilir area, South Sumatera. All chemicals are in analytical grade.

2.2 Methods

Design of Optimum Formula

Tablets were made according to the best formula from previous studies using starch as a disintegrant and PVA as a binder (Fitrya, 2016). Optimization of tablet formula was designed using a *simplex lattice design* (DX®8 software, USA). The independent variables are the concentration of binder and disintegrant while the dependent variables are the physical properties and dissolution of tablets. The starch is in a range of 5-20% (Bhowmik et al., 2010) and PVA is less than 2% (Saxena, 2004). Therefore, PVA is 1% and 2% for low and high levels, respectively. Based on the simplex latice design, 8 tablet formulas were produced (Table 1).

The extract was mixed with lactoce until reaching homogen. The disintegrant, adsorbent, and binder were added sequently. Produced granules were dried at 40-50°C until constant weight, and they were then sieved with No. 14. The dry granule was added magnesium stearate and talcum as lubricant. The resulting granules were evaluated for their physical properties, such as the hausner's ratio, compressibility index, flowability, angle of repose and water content (Ermawati et al., 2017). The granules were evaluated following the British Pharmacopoeia, 2008. Finally, the granules were pressed into tablets by tableting machine (DTR 4). An optimimum formula was determined based on a formula producing tablets with the best physical properties and dissolution.

The Physical Properties Evaluation of Tablets

The physical properties of tablet studies included organoleptic, thickness, weight variation, hardness, friability, disintegration time, and dissolution (Kharisma et al.; Mishra, 2019). The friability of tablet referred to the British Pharmacopoeia, 2008 using friability tester (CS-1 Friability Tester). Tablet uniformity and disintegration time were determined referring to Indonesian Pharmacopeia 4^{nd} by disintegration tester (BJ-3 Disintegration Tester), while tablet hardness was determined referring to the United States Pharmacopeia 32^{nd}, 2009 by a hardness tester (YD-1 Hardness Tester). Experiment results were statistically analyzed by SPSS®21.

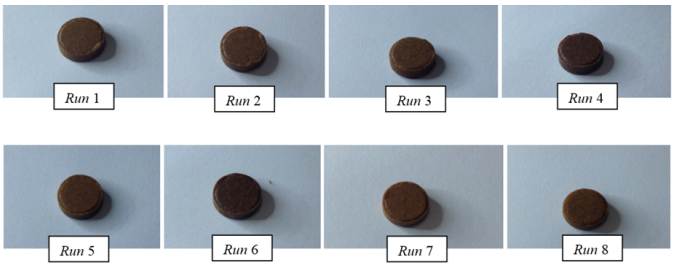

Figure 1. Tablet run 1-8

In Vitro Dissolution Study

The optimum formula dissolution was tested referring to the British Pharmacopoeia, 2008 using the dissolution tester (RC-3 Dissolution Tester) by determining a total phenolic content as a marker. The total phenolic content was measured by the Folin-Ciocalteu's method.

3. RESULTS AND DISCUSSION

3.1 Granules Properties

Experimental design of tablet formula using DX®8 software was produced eight formulas (F_1-F_8) showed in Table 1.

A wet ganulation method was used based on consideration of characteristics of the extract, such as viscousity and hygroscopy. In addition, by the wet granulation method, flow properties and compressibility of powder can be improved so that the powder can be more easily compressed into tablets.

Quality all of granule formulas, that is determined by repose angle, hausner ratio and compressibility index, can be categorized from good to excellent in their flow properties as presented on Table 2 (Mishra, 2019). Moreover, the plant extracts tend to be more hygroscopic and low flowability. These excellent flow properties become a main specification for weight uniformity during compression of tablets (Son et al., 2018).

3.2 Physical Properties of Tablets

Tablet formulas 1–8 from the experimental design are shown in Figure 1. The physical properties of these tablets are presented in Table 3.

Weight variations of these eight formula tablets were in a range of 0.50–0.52 g. These variations indicated all batches in weight uniformity, and each batch content is uniform. The mathematical models for responses as tablet characteristics from the DX®8 software are presented in Table 4.

As indicated in Table 4, starch and PVA concentration influenced tablet characteristics (except friability) i.e., weight, thickness, hardness, and disintegration time. In the mathematical models, a positive coefficient influenced responses synergistically, while a negative coefficient showed an antagonistic effect on the responses (Rao et al., 2009). Moreover, the starch and PVA concentration individually influenced weight and thickness responses while the interaction between both concentration did not have effects. Increase in starch and PVA

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Table 1. Experimental Design of Optimized Formula

Runs	Concentration (%) Starch	PVA	Extract (mg)	Lactose (mg)	Aerosil® (%)	Talc (%)	Mg Stearate (%)
F1	17.5	1.25	135	260.49	0.5	1	0.5
F2	12.5	1.75	135	282.99	0.5	1	0.5
F3	10	2	135	294.24	0.5	1	0.5
F4	15	1.5	135	271.74	0.5	1	0.5
F5	20	1	135	249.24	0.5	1	0.5
F6	15	1.5	135	271.74	0.5	1	0.5
F7	20	1	135	249.24	0.5	1	0.5
F8	10	2	135	294.24	0.5	1	0.5

Table 2. The Granules Properties Evaluation Results

Formula (Runs)	Hausner ratio ± SD	Compressibility index (%) ± SD	Flowability (10 g/s) ± SD	Angle of repose (°) ± SD	Water content (%) ± SD
1	1.14 ± 0.06	12.23 ± 4.78	1.62 ± 0.16	28.0 ± 2.92	7.92 ± 3.67
2	1.10 ± 0.00	9.02 ± 0.12	1.97 ± 0.06	26.7 ± 1.05	8.05 ± 1.40
3	1.15 ± 0.01	12.9 ± 0.42	2.20 ± 0.26	30.07 ± 2.29	5.88 ± 1.40
4	1.10 ± 0.03	9.42 ± 2.16	2.20 ± 0.26	29.58 ± 3.48	7.19 ± 0.51
5	1.14 ± 0.02	11.9 ± 1.16	2.30 ± 0.10	31.07 ± 1.89	6.18 ± 1.47
6	1.10 ± 0.03	9.42 ± 2.16	2.20 ± 0.26	29.58 ± 3.48	7.19 ± 0.51
7	1.14 ± 0.02	11.9 ± 1.16	2.30 ± 0.10	31.07 ± 1.89	6.18 ± 1.47
8	1.15 ± 0.01	12.9 ± 0.42	2.20 ± 0.26	30.07 ± 2.29	5.88 ± 1.40

concentration would increase weight of tablets because molecular weights of the starch and PVA are 300–1000 g/mol and 20.000–200.000 g/mol, respectively (Rowe et al., 2009). Mean while, the differences in the tablet thickness were due to the differences in pressure during the pressing process (Rao et al., 2009).

Friability was tested to assess effects of friction and shocks, which may often cause breaking, capping, or cracking tablet (Hardenia et al., 2016; Zade et al., 2009). According to BP 2008 a good friability value is less than 0.8%, the tablets were therefore indicated a good mechanical resistance. Low friability indicated that the tablet has resistance to friction and is able to maintain its shape. While the tablet surface has been eroded in high friability (Kharisma et al.). Furthermore, hardness was tested to describe tablet endurance through good mechanical resistance for packing and distribution. The individual component of the starch and PVA and their interactions significantly increased hardness and disintegration time. On the other hand, factor of disintegrant and binder and interaction of both could insignificantly reduce the friability of tablet. The starch has more effect on tablet hardness compared to PVA. The hardness can also be influenced by a compression force during manufacturing, pressing speed, and a height - diameter ratio of the tablets (Adeleye et al., 2015). As starch tend to deform, increasing the starch concentration allows blends more compact (Bhowmik et al., 2010). In addition, the using more PVA caused an increase in hydroxyl groups to binding the other tablet component. Based on response equations in Table 4, starch concentration become a dominant factor influencing hardness.

Increasing starch, PVA, and their interaction accelerated the disintegration time. Based on their coefficients, PVA had the most effect on disintegration time compared to starch and their interaction. During the disintegration process, the capillary bridges were formed causing adjacent particles to attract each other. The disintegration capability must exceed interparticulate forces and destruct the bonds. Penetration of liquid into tablet pores is the first step and often determines the rate of tablet disintegration (Markl and Zeitler, 2017). Increasing starch concentration would also improve a wicking mechanism and deformation recovery, resulting in a faster disintegration time. PVA has a high tendency to swell in water and biological liquid (Kadajji and Betageri, 2011). The hydroxyl groups in the PVA molecules which are close each other will interact to form intra and intermolecular hydrogen bonds. This hydrogen bond results in crystal formation. Increase in crystallinity in the swelling polymer reduces the disintegration ability (Muppalaneni, 2013; Markl and Zeitler, 2017).

3.3 In Vitro Dissolution Study

A drug release profile of tablets in vitro was observed by percentages of the drug release for 60 minutes (DE_{60}) as presented in Figure 2.

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Table 3. The Physical Properties of Tablets

Batch	Weight (g) ± SD	Thickness (mm) ± SD	Friability (%)	Hardness (N) ± SD	Disintegration time (mnt) ± SD
1	0.51 ± 0.01	3.36 ± 0.15	0.3	19.33 ± 3.15	11.79 ± 1.88
2	0.52 ± 0.01	3.32 ± 0.06	0	27.33 ± 1.65	16.47 ± 1.87
3	0.51 ± 0.01	3.56 ± 0.13	0	17.53 ± 3.02	28.67 ± 2.12
4	0.52 ± 0.01	3.48 ± 0.07	0	29.18 ± 2.17	29.16 ± 1.13
5	0.51 ± 0.02	3.41 ± 0.16	0	35.52 ± 4.04	15.65 ± 1.10
6	0.52 ± 0.02	3.48 ± 0.05	0	30.53 ± 3.62	29.24 ± 2.64
7	0.50 ± 0.01	3.36 ± 0.11	0.15	34.52 ± 3.12	15.93 ± 1.24
8	0.51 ± 0.02	3.58 ± 0.10	0	13.92 ± 0.77	30.93 ± 4.23

Table 4. Mathematical Models of Responses

Respons (Y)	SLD actual component equation Models of respons	*P value*
Weight variation	Y = 0.50 (A) + 0.51(B) + 0.05 (A)(B)	0.02
Thickness	Y = 3.38(A) + 3.57(B) + 1.00(A)(B) + 0.70(A)(B)(A-B) - 3.96(A)(B)(A-B)^2	0
Friability	Y=0.07(A) + 0.00(B) - 1.00(A)(B) + 1.40(A)(B)(A-B) - 3.00(A)(B)(A-B)^2	0.11
Hardness	Y= 35.02(A) + 15.72(B) + 56.31(A)(B) – 94.12(A)(B)(A-B) - 153.62(A)(B)(A-B)^2	0
Disintegration Time	Y= 15.79(A) + 29.80(B) + 25.62(A)(B) + 12.40(A)(B)(A-B) – 287.33(A)(B)(A-B)^2	0

A = starch concentration and B = PVA concentration

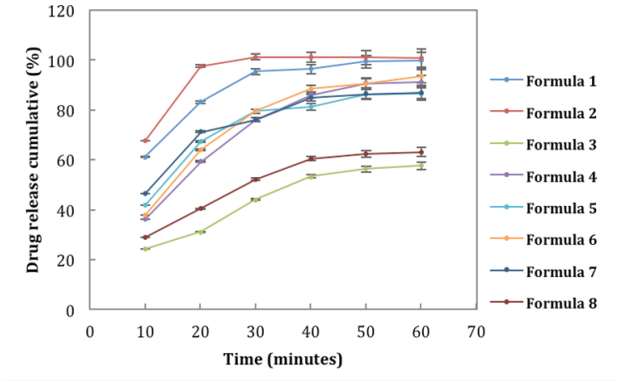

Figure 2. Dissolution Curve of Formula 1–8

The mathematical model recommended was quartic with p value less than 0.05 This model indicates that two components (A and B) have a significant effect on DE_{60} of tablets. The SLD actual components are given in Equation 1.

$$Y = 67.21(A) + 42.65(B) + 46.71(A)(B)\text{˜}118.71 (A)(B)(A-B) + 469.11(A)(B)(A-B)^2 \quad (1)$$

From Eq. 1, starch and PVA increase DE_{60} of tablets, and starch has more significant effects than PVA. Increasing starch concentration formed capillary pathways that were getting bigger. Moreover, the starch became more liquid penetrating into the tablet, and disintegration time of tablet was then faster. In addition, an increase in starch concentration resulted in more disintegrating particles undergoing deformation. Increasing the distintegration time accelerated the dissolution rate of the tablet (Kumar et al., 2016).

3.4 Optimum Formula

Optimum formula was determined based on dependent variable responses. Responses priority are from 1 (low) to 5 (high). The weight, thickness, friability, and disintegration time of tablets responses were selected in a minimum priority, while the hardness response was selected for level 3 (medium). The less weight and thickness tablet was, the easier it swallowed. If the tablet was too hard, tablet disintegration was postponed and dissolution was bad. Meanwhile, less hard tablets would be easier to break down them for packing and distributing. The faster disintegration time of tablets was, the better the dissolution of tablets would be. The tablet dissolution is selected in a maximum priority, because the dissolution profile is important parameter ensuring a drug bioavailability. The faster dissolution rate would result in better drug absorptions.

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DX®8 analysis obtained three proposional combinations of the starch and PVA, and the largest desirability value (0.777) was selected. This optimum composition consisted of 19.5% starch and 1.05% PVA. If the starch concentration was under this optimum level, capilariy pathways would be not formed. In contrast, if the concentration was too much, the tablet compressibility became too bad (Bhowmik et al., 2010).

Disintegration time of tablet was long when the PVA concentration was 2%. The PVA has many hydroxyl groups in its structure, so that it has a capability as binder. Therefore, higher concentration of PVA resulted in more hydroxyl groups interacting with the extract components. The PVA binded either the extract or other components of tablet by hydrogen bonds, dipole-dipole interactions, and van der waals's bonds.

4. CONCLUSIONS

The starch and PVA concentration significantly influenced the tablet characteristics. Based on characteristics and dissolution analysis, the optimum concentration of the starch and PVA on tablet formula are 19.5% and 1.05%, respectively. In order to use dry extracts for making a tablet, we suggest to reduce extract moisture and to improve flow properties of the granules.

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