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Abstract

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ABSTRACT

Tunjuk langit rhizome *(Helminthostahcys zeylanica (Linn) Hook*) has been used traditionally as an anticancer and antiinflammatory agent. Previous studies have proved the potency of ethanol extract from this rhizome as an antihyperuricemic agent. In this study, the ethanol extract of the rhizome, was formulated into tablet dosage forms by a wet granulation method. Three tablet formulas with different types of disintegrant and binder were formula A (starch: PVA), formula B (Avicel®PH102: PVP), and formula C (sodium alginate: methylcellulose). Physical properties (such as weight variation, tablet diameter, thickness, friability, hardness, and disintegration time) and dissolution of tablets were evaluated. The analysis results showed that formula A produced the best physical properties and dissolution characteristics.

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INTRODUCTION

Tunjuk langit (TL) rhizome (*Helminthostachys zaylanica*) has been traditionally used as medicine for liver diseases (Suja, 2004). In South Sumatera TL were used as an anticancer and anti-inflammatory agent. Several studies on chemical constituents of TL rhizome showed that the rhizome contained flavonoid ugonin A-D (Murakami, 1973), flavonoid ugonin E-L (Huang, 2003; Fitrya 2010), ugonstilbene A-C (Chen, 2003).

Pharmacology activity studies of the extract and isolated compound of TL rhizome proved that the ethanol extract of TL possess effects of aphrodisiac (Suja 2002), hepatoprotective (Suja, 2004), antioxidant (Huang, 2003; Fitrya, 2011), neuroprotective (Chien et al, 2009) and antiinflamation (Yaun-Chao-Huang *et al*, 2009). Ugonin J and K had activity to murine leukemia cell P-388 (Fitrya, 2009).

Our preclinical study showed that the extract ethanol of TL has a hipourisemia effect with ED_{50} value of 135,76 mg/kg BB (Fitrya, 2014). Standardization of the ethanol extract exhibited good in a range result (Fitrya, 2013). In this paper we formulated the ethanol extract of TL rhizome by a wet granulation method by using different types of disintegrant and binder.

MATERIAL AND METHODS

The Tunjuk langit rhizome was obtained from Sekayu, South Sumatera. Lactose, Aerosil®, magnesium stearate, talcum, Avicel PH® 102, starch, methyl cellulose, sodium alginate, polivynil alcohol, and polivynil pirolidon were all purchased from Bratachem.

Three-tablet formulas from ethanol extract of TL rhizome (Table 1) were produced by a wet granulation method. The ethanol extract of TL rhizome was mixed with lactose, different types of disintegrants, and adsorbent, forming a homogeneous mixture. Addition of varied type of binder was also conducted to produce a solid mass. Granules were dried in oven at 40-60°C to a constant mass. Dried granules were incorporated with magnesium stearate and talcum as lubricating agents. Physical properties of granules were evaluated which include moisture content, compressibility, flow ability, and repose angle. Tablets were prepared by compressing the granules using Hydraulic Hand Press single punch tabletting machine (DTR 4).

Furthermore, physical and dissolution characteristics of tablet were evaluated, including

weight variation, dimension variation, friability, hardness, disintegration time, and dissolution time.

Table 1. Tablet Formulas of Ethanol Extract from TL Rhizome

Component	Formula A	Formula B	Formula C
Extract	135,76 mg	135,76 mg	135,76 mg
Disintegrant	Amylum 10%	Avicel® PH102 10%	Potasium alginat 10%
Binder	PVA 2%	PVP 2%	Methyl cellulose 2%
Filler	Lactose 67,92%	Lactose 67,92%	Lactose 67,92%
Adsorbent	Aerosil® 0,5%	Aerosil® 0,5%	Aerosil® 0,5%
Glidant	Mg stearate 0,5%	Mg stearate 0,5%	Mg stearate 0,5%
	Talcum 1%	Talcum 1%	Talcum 1%

Twenty tablets of each formula were weighed with electronic weighing balance and the average of weight was calculated. Each tablet was then weighed separately to determine standard deviation of each formula.

Dimensional homogeneity was obtained by measuring the diameter of 20 tablets with a calliper. Standard deviation was then calculated to determine the homogeneity.

6.5 g of tablets were weighed and put in *friabilator tester* at a speed of 25 rpm for 4 minutes. The friabilated tablets were reweighed to calculate the percentage of weight loss.

Hardness of tablet was determined using the hardness tester YD-1 type. One by one of six tablet samples were put upright inside the hardness tester to measure the force required to break the tablet.

The disintegration time of tablets was determined by using the disintegration tester BJ-3 type. Six tablets randomly selected were used for the test. The disintegration medium was 1000 mL aquadest maintained at 36^{o}C – 38^{o}C.

The dissolution test of tablets was determined at 37 ± 0,5^{o}C by using the Dissolution Test Apparatus Type 2 (RC-3 Dissolution Tester) with rotation speed of 50 rpm in 900 mL of HCl 0,1 M for 60 minutes. Five mL samples were withdrawn and replaced with fresh medium at fixed time intervals of 10, 20, 30, 40, 50, and 60 minutes.

The samples were diluted and the amount of drug released was determined by UV-Vis spectrophotometer at a maximum wavelength. Dissolution parameters were interpreted by a dissolution efficiency (DE) method. Statistical analysis of the data was carried out using SPSS® 21 to compare analysis results of tablets A, B and C.

RESULT AND DISCUSSION

The evaluation of granules was conducted to determine physical properties, such as Hausner ratio, compressibility, flowability, and moisture contents of granules. Table 2 shows that all three tablet formulas produced granules with good flowability with value less than 10 g/s (British Pharmacopoeia, 2008). The angle of repose is important to see the friction of granules, which less friction results in good flowability. All three formulas produced granules with good repose angles.

Moisture contents of granules were 2 – 5%. A granule with too high or too low moisture contents results in compression problems such as cracking and sticking (Aulton and Taylor, 2013). The evaluation result of the compressibility, flowability and moisture content of the granules is satisfied and complies with requirements in Table 2.

Table 3 shows that the standard deviation of the tablet A, B and C were not high and all three formulas produced tablets which comply with the Farmakope Indonesia regulation in a tablet weight variation.

Table 2. Granules Properties of Formula A, B, and C

Evaluation	Formula		
	A	B	C
Hausner ratio ± SD	1,14 ± 0,07	1,11 ± 0,02	1,08 ± 0,03

Compressibility Index(%) ± SD	11,93 ± 5,40	9,99 ± 1,19	7,19 ± 2,29
Flowability (10g/s) ± SD	1,65 ± 0,15	1,56 ± 0,14	1,06 ± 0,03
Angle of repose (°) ± SD	28,81 ± 0,44	29,95 ± 1,24	28,63 ± 2,06
Moist Content (%) ± SD	2,89 ± 1,74	2,87 ± 0,02	5,02 ± 1,37

Table 3. Organoleptic and physical properties of tablet A, B and C

Evaluation Results	Tablet			Requirement
	A	B	C	
Organoleptic	Dark brown, a distinct scent of extract, smooth surface	.Dark brown, a distinct scent of extract, smooth surface	.Dark brown, a distinct scent of extract, smooth surface	In accordance to Farmakope Indonesia III
Weight (g) ± SD	0,51 ± 0,00	0,53 ± 0,00	0,50 ± 0,00	
Diameter (mm) ± SD	12,02 ± 0,01	12,00 ± 0,00	11,91 ± 0,03	
Thickness (mm) ± SD	3,23 ± 0,00	3,42 ± 0,05	3,18 ± 0,02	
Friability (%) ± SD	0,15 ± 0,26	0,00± 0,00	0,39 ± 0,23	< 0,80%
Hardness (N) ± SD	17,37 ± 2,25	30,40 ± 2,56	40,68 ± 5,65	
Disintegration time (min) ± SD	18,38 ± 1,79	58 ± 8,65	61,38 ± 5,54	< 15 minutes

Annotation :A (starch: PVA), B (Avicel® PH102: PVP), and C (Sodium alginate: methyl cellulose).

A dimension range of produced tablets was 11,91 - 12,02 mm with a thickness range of 3,18 – 3,23 mm. A friability evaluation showed that three of tablets fulfill a friability qualification with a value of less than 0,8% (British Pharmacopea, 2008). The tablet formulation using PVP as binder have less friability than using Methocel®, acasia, and methyl cellulose (Cutt *et al*. 1986; Joneja *et al*. 1999;

Nagadivya, 2012). The hardness value of tablets in a range of around 17.37 – 40.68 N showed that the tablets have enough hardness.

Formulas C produced the hardest tablet due to the strong binding properties of sodium alginate and its interaction with methyl cellulose.

The evaluation of tablets distintegration time showed that all formulas produce tablets with the disintegration time more than 15 minutes, which did not fulfill the Farmakope Indonesia IV qualification. Tablet C showed the longest disintegration time using methyl celluloce as binder and sodium alginate as disintegrant. Sodium alginate is salt of alginic acid with a high absorption capacity of alginate (Kumar *et al*. 2010), which causes the alginate to absorb the ethanol extract of TL and produces strong bonding interaction (*intermolecular and electrostatic forces*). This interaction caused alginate capability to absorb water; therefore, the alginate decreased swelling activity to disintegrate the tablets. Tablet B with PVP as binder and Avicel® PH102 as disintegrant also showed a long disintegration time. PVP have high binding capacity as binder in wet granulation. Moreover as disintegrant, Avicel® PH102 could act as filler-binder to granules. The usage of Avicel® PH102 10% and capability of PVP as binder caused tablet B have a long disintegration time.

Tablet A produced by using PVA as binder and amylum as disintegrant is the most satisfied formula with the disintegration time of 18,38 ± 1,79 minutes. PVA have a lot of hydroxyl group, which provides PVA with the ability to create hydrogen bond by another group from extracts or compounds by dipole interactions (Betageri and Kadajji, 2011). A disintegration mechanism of starch was by penetration of water into tablets through pores and capillary actions. This process weakens intermolecular bonding of particles and causes tablets to disintegrate.

The dissolution test was interpreted by using a dissolution efficiency (DE) method which describes a dissolution process at the dissolution curve which has a correlation with in vitro and in vivo test (Khan, 1975). The results of this dissolution test exhibited effects of different binder and disintegrant types on the dissolution. The tablet A has the best value of DE_{60} at 89 ± 4.61% (Table 4), which is contributed by its faster disintegration time. DE_{60} value of tablet C was 34 ± 4.71%, this value was low due to interactions of sodium alginate, methyl celluloce and ethanol extract, which retards disintegration

process. Tablet B also exhibited a poor dissolution profile with DE_{60} value of 24.99 ± 2.84%, caused by high binding capability of PVP and interaction between Avicel® PH102 and ethanol extract of TL.

Table 4. DE_{60} value of tablet A, B, and C

Tablet	DE_{60} (%) ± SD
A	89 ± 4,61%
B	24,99 ± 2,84
C	34,00 ± 4,71

CONCLUSION

The wet granulation method was suitable to develop the TL extract into tablet. Formula A using starch as disintegrant and PVA as binder produced the best formula with desirable physical properties and dissolution characteristics.

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