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Influence of Various Concentrations of Pvp K-30 As A Binder on The Physical Quality of Cerme (*Phyllanthus acidus*) Leaves Extract Tablet

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Abstract
A study on the influence of tablet formulae containing cerme leaves extract using PVP K-30 as a binder in the concentrations of 2% (formula A), 3% (formula B), 4% (formula C) on the physical quality of tablet has been conducted. *Cerme* leaves extract was obtained by percolation method employing ethanol 96% as a solvent. Tablets were prepared by wet granulation method and the physical quality of resulting granules was evaluated including moisture content, repose angle, flow rate, and compressibility. Granules were then compressed to yield tablets of 650 mg, in which each tablet contains 449 mg of dry extract of *cerme* leaves. The physical quality of resulting tablets was evaluated including weight uniformities, hardness, friability, disintegration time, dissolution, and a comparative qualitative determination of chemical contents of cerme leaves extract by TLC (Thin Layer Chromatography) in various samples commencing from viscous extract until tablet dosage form. The hardness, friability, disintegration time, and dissolution data were evaluated using completely randomized design ANOVA with a level of confidence of 95%, and subsequently followed by LSD (Least Significant Difference) test. It can be concluded that *cerme* leaves extract could be formulated as a tablet and met the physical quality requirements of tablet. There were no significant differences on the hardness and dissolution of three formulae tablets ($F_{calc} < F_{table}$). On the other hand, the friability and disintegration time of three formulae tablets differed significantly ($F_{calc} > F_{table}$). Formula A was the selected one owing to its shortest disintegration time and highest economic value (least binder concentration).
Key words: Cerme (*Phyllanthus acidus*) leaves extract; Tablet formulation; Physical quality of tablet; Binder; PVP K-30.

Background

Obesity may cause a serious problem since it can lower someone's self-esteem and result in various diseases including: cardiovascular, gall bladder, and diabetes. The causes of obesity, among others, are excessive food consumption, exercise patterns, psychological and genetic factors, as well as metabolic abnormalities. Various techniques to handle obesity include diet, exercise, psychotherapy and medication intervention using appetite suppressants (Guyton, 1997).

One type of plant that can lower the body weight and reduce the appetite is *cerme (Phyllanthus acidus)*. It is known that the viscous extract of *cerme* leaves at a dose of 1 g/kg bw may reduce body weight and epididimus lipid of albino Wistar rats. The administration of cerme leaves infusion can also reduce the body weight without decreasing the appetite and this infusion is not toxic in mice (Alfiah, 2000).

The leaves, bark and stem parts of *cerme* contain saponins, flavonoids, tannins and polyphenols (Hutapea, 1994; Sastroamidjoyo, 2001). It was hypothesized that tannins may demonstrate slimming effect by precipitating mucosal proteins in the intestine and hence, reducing the absorption of food (Robinson, 1995). The content of tannins in *cerme* leaves extract can be determined by permanganometry titration method (Anonymous, 1989).

Frequent problems arising from the administration of traditional medicine are unpleasant taste and odor, less practical use and less precise dose (Yaputra, 1989). Development of science in pharmaceutical technology field has resulted in a rapid development of the dosage form. Extract can be formulated into various dosage forms such as granules, tablets, capsules and syrup. Tablet is selected because it can mask the unpleasant odor and taste. Tablet physico-chemically is more stable than syrup, it has a solid shape and small volume so that it is easily packaged, stored and transported, and is not easily contaminated by microbes (Allen *et al.*, 2011).

Cerme leaves extract is hygroscopic, sticky, poor compressibility, has a characteristic taste and odor. Therefore aerosil should be incorporated as a desiccant in the preparation of *cerme* dry extract. Wet granulation method is selected in the preparation of tablet since the chemical contents in *cerme* leaves are relatively stable to temperature and humidity. Binders play a significant role in wet granulation method, by binding all particles in the formula to form granules subsequently compressed into a good. PVP K-30 is widely used as a binder in tablet formulation because it is freely soluble in water and organic solvent, stable, non-toxic and non-allergic in the clinical use. As a binder, PVP K-30 is generally used at a concentration of 0.5-5% (Rowe *et al.*, 2009). In

tablet formulation, PVP K-30 can be employed in the solution form or dry powder subsequently followed by the addition of wetting liquid. The amount of binder in the formula can affect the strength of granules and hence, influencing the physical quality of the resulting tablets. Cholifah (2003) reported that PVP K-30 at high concentrations increase the hardness and prolong the disintegration time of tablet. This will in turn reduce the amount of dissolved drug. Thus the determination of optimum concentration of PVP in the formula is necessary. In this study, PVP K-30 at various concentrations of 2, 3 and 4% were employed as a binder in tablet formula containing cerme leaves extract. The physical quality of resulting tablets including hardness, friability, disintegration time and dissolution was observed. It is expected that *cerme* leaves extract tablet formula conforming the physical quality requirements of tablet could be obtained.

Material and Methods

Materials and Apparatus

Cerme leaves were obtained from Nongkojajar region East Java grown in a land of approximately 300 m above sea level with rainfall of approximately 2271 mL/year. Prior to the study, *cerme* leaves were characterized by the UPT Materia Medica Batu-Malang East Java Provincial Health Council.

The experimental materials of pharmaceutical grade included magnesium stearate, talcum, aerosil, PVP K-30, sodium starch glycolate, dibasic calcium phosphate and kaolin. The following materials, including $KMnO_4$, H_2SO_4, oxalic acid, sodium hydroxide, iodine, $FeCl_3$, HCl and indigo carmine, were of pro analytical grade.

Equipments used in this study were tabletting machine single punch, tablet hardness tester (Schleuniger 6D-30 type, Germany), tablet friability tester (Erweka TA-3 type, Germany), disintegration apparatus (Erweka ZT 3-1 type, Germany), moisture analyzer (Sartorius MA 30 type, Germany), analytical balance (Toledo Metler AL 204 type, Germany), glass apparatus and other supporting equipments.

Preparation of Crude Material

The leaves were washed and rinsed, and then dried in a shady aerated place. The dried leaves were grounded and sieved through a no. 4/8-mesh siever.

Extraction Method

The extraction method employed in this study was percolation using 96% ethanol, with a flow rate of 1 mL/min. The resulting percolate was evaporated on a water bath at a controlled temperature of less than 50 °C.Twenty-five grams of aerosil was added into the resulting viscous extract, and dried in an oven at a temperature of 50 °C, to obtain a dry extract subsequently grounded and sieved through a-100 mesh siever.

Dose Calculation

Cerme leaves extract was administered at a dose of 1 g/kg bw may reduce the body weight and epididimus lipid as well as alter triglyceride level in rats.

Dose in human = rat dose ×conversion factor (= 1/1000 × 200 × 56) = 11.2 g/70 kg daily

The body weight of Indonesian people is generally 60 kg

[60/70] × 11.2 g = 9.6 g/60 kg bw of viscous extract daily

Dose = [dry extract/viscous extract] × dose of viscous extract (= 96.85/115 × 9.6) = 8.08 g/day

In this study, each tablet contained dry extract of *cerme* leaves of 0.449 g and six tablets were administered three times daily. Cerme leaves extract tablets was prepared into three different formulae by wet granulation method using PVP K-30 at concentrations of 2% (FA), 3% (FB) and 4% (FC) as a binder. Each formula consisted of 100 tablets and prepared in triplicates.

Formula tablets are shown in Table 1.

Table 1. Tablet formula of cerme leaves extract

No.	Compositions	Formula A (mg)	Formula B (mg)	Formula C (mg)
1.	*Cerme* leaves extract	449	449	449
2.	Dibasic calcium phosphate	123	116.5	110
3.	Sodium starch glycolate	32.5	32.5	32.5
4.	PVP K-30 (2, 3 and 4%)	13	19.5	26
5.	Talcum (4%)	26	26	26
6.	Magnesiumstearate (1%)	6.5	6.5	6.5
	Total weight	650	650	650

Tablet Manufacturing Process

Dry extract was mixed with dibasic calcium phosphate, sodium starch glycolate (5%) until homogeneous. A solution of PVP K-30 was added to form a damp granule mass,then was sieved through a-16 mesh siever and dried in an oven at a temperature of 50 °C. Dried granules were re-sieved through a-20 mesh siever and then mixed with 4% of talcum and 1% of magnesium stearate. The physical quality of mixed granules was evaluated including: moisture content, flowability, repose angle and compressibility index. Granules of good quality were compressed using a tabletting machine with a-13 mm diameter of molds and a tablet weight of 650 mg. The quality of resulting tablets was evaluated including: weight and size uniformities, friability, disintegration time and dissolution rate of tablets.

TLC Chromatogram Profiles

To evaluate the stability of chemical contents in *cerme* leaves during tablet manufacturing process, a TLC study was performed in the stages of extraction process, drying process, and tabletting.

Preparation of Test Samples

Extract powders, granules and tablets of each formula were weighed (650 mg), dissolved in 96% ethanol up to 10 mL, filtered, and the first filtrate was discarded whereas the subsequent filtrate was collected. Ten microliters of filtrate was applied onto a-GF_{254} silica plate and eluated using a mixture of n-hexane : ethyl acetate (4:1, v/v) with a development distance of 8 cm. The spot was observed using visible light, UV 254 and 366 nm. Following the above observation, the spot was sprayed using vanillin sulphate as a spraying reagent, dried and observed using visible light, UV 254 and 366 nm. The Rf value was 0.2-0.5 cm (Kirchner, 1978).

Results and Discussion

The parts of plant used in this study were fresh and green *cerme* leaves. To ensure the type of plant employing in this study, the *cerme* leaves were characterized by the UPT Materia Medica Batu-Malang East Java Provincial Health Council.

Prior to extraction, *cerme* leaves powder was subject to several crude standardization tests including: organoleptic, ash content, loss on drying, and chemical identification as shown in Table 2. The results indicated that the crude material met all the requirements (Anonymous, 1989).

Table 2. The results of crude material of *cerme* leaves powder

No.	Analysis	Reference	Result	Remarks
1.	Organoleptic:			
	- Color	Brownish green	Brownish green	Conformed
	- Odor	Typical aromatic	Typical aromatic	Conformed
	- Taste	Chelate/tasteless	Chelate/tasteless	Conformed
2.	Ash content	Less than 7%	5.44%	Conformed
3.	Loss on drying	Less than 10%	8.60%	Conformed
4.	Identification			
	+ 5 drops of concentrated H_2SO_4	Brown	Brown	Conformed
	+ 5 drops of concentrated HCl	Green	Green	Conformed
	+ 5 drops of 5% w/v NaOH	Yellow	Yellow	Conformed

The extraction process employed in this study was percolation using 96% ethanol, to maintain the stability of active compounds in the crude material owing to the absence of heating process. The testing result of viscous extract is presented in Table 3.

Table 3. Examination results of viscous extract

No.	Observation	Reference	Remarks
1.	Color	Brownish green	Conformed
2.	Odor	Typical aromatic	Conformed
3.	Consistency	Viscous	Conformed

Aerosil was added into the resulting viscous extracts and subsequently dried in an oven with a temperature of 50 °C until dry. This resulting dry extract was used as an active ingredient in the tablet manufacturing process. Each tablet contained 449 mg of dry extract.

Wet granulation method using PVP K-30 as a binder at concentrations of 2% (FA), 3% (FB), and 4% (FC) was selected. To identify the compressibility and flowability characteristics of granules, several tests were performed, as shown in Table 4.

Table 4. The quality of granules

No.	Parameters	Requirements	FA	FB	FC
1.	Moisture content	2-5%	4.48 ± 0.20	4.44 ± 0.22	4.75 ± 0.42
2.	Flow time	< 10 seconds	9.15 ± 0.03	7.77 ± 0.10	9.44 ± 0.13
3.	Repose angle	20-40°	31.45 ± 0.03	31.78 ± 0.05	31.15 ± 0.06
4.	Compressibility (%)	5-18%	13.73 ± 0.59	14.10 ± 0.72	13.80 ± 0.56

The results showed that FA, FB and FC met the quality standard of good granules, namely the moisture content of 2-5% (Bandelin & Shangraw, 1989; Voigt, 1995), the flow time of less than 10 seconds (Voigt, 1995), the repose angle of 20-40° (Marshall, 1996), compressibility of 5-18% (Fierse & Hagen, 1996).

Good quality of tablets should meet the quality requirements as desired, including weight and dose uniformities, lack of incompatibilities, attractive appearance, as well as possible and efficient large scale production (Bandelin & Shangraw, 1989). The examination results of the quality of *cerme* leaves extract tablet are shown in Table 5.

Based on data shown in Table 5, FA, FB and FC demonstrated good weight uniformity since none of the tablets showed weight deviations of more than 5% and all of them passed the size uniformity test. The diameters of tablet were of no more than three times and of no less than 4/3 times of tablet thickness (Anonymous, 1979).

Table 5. The quality testing of tablets

No.	Parameters	Requirements	FA	FB	FC
1.	Weight uniformity	X ± 5%	648 ± 0.20	654 ± 0.22	652 ± 0.42
2.	Thickness	4.33-9.73mm	4.42 ± 0.03	4.43 ± 0.10	4.42 ± 0.13
3.	Hardness	4-8 kgf	5.99 ± 0.48	6.03 ± 0.50	6.17 ± 0.35
4.	Friability	≤ 1%	0.58 ± 0.03	0.38 ± 0.03	0.18 ± 0.03
5.	Disintegration time	< 15 minutes	13.26 ± 0.08	14.20 ± 0.05	14.92 ± 0.10
6.	Tannin level	-	10.67 ± 0.08	10.59 ± 0.08	10.56 ± 0.08
7.	Dissolved tannins	Q45>75%	97.69 ± 0.08	97.83 ± 0.08	97.96 ± 0.08

Tablet hardness is the force required to break or crush tablets and expressed in a kilogram force unit. According to Parrot (1971) a good hardness of tablet should vary between 4-8 kgf. The results showed an increased concentration of PVP K-30 may enhance the hardness of tablets although they did not differ significantly by one-way ANOVA ($p<0.05$).

Tablet friability test is used to determine the extent of tablet resistance toward friction and shocks experienced during manufacturing, packaging and transportation.The results showed that FA, FB and FC had good friability because its value was of less than 1% (Banker & Anderson, 1996). Statistical analysis by one way ANOVA showed no significant difference in the tablet friability among formulae ($p < 0.05$).

Disintegration time is an important parameter for an oral tablet since it may affect the oral bioavailability. Tablet is claimed to be completely crushed if the remaining preparations left on the apparatus screen is a soft mass which does not have a clear core. Tablet disintegration time should be of no more than 15 minutes (Anonymous, 1979). The experimental results demonstrated that FA, FB and FC met the requirements. An increased concentration of PVP K-30 prolonged the disintegration time of *cerme* leaves extracts and there was a significant difference in the disintegration time among tablet formulae by one way ANOVA ($p < 0.05$).

Dissolution test results showed that FA, FB and FC met the requirements according to Shargel & Yu (1999), that is the percentage of released drug is 75% within 45 minutes. There was no significant difference in tablet dissolution among formulae by one way ANOVA ($p<0.05$) and this may be due to a small difference in the concentrations of PVP K-30 as a binder among FA. FB and FC.

Figure 1. Chromatogram of constitutents in *cerme* leaves extract, from crude materials until tablets following observation under UV 366.Notes: 1. Crude materials; 2. Viscous extract; 3. Dry extract; 4. FA granules; 5. FB granules; 6. FC granules:7. FA tablet; 8. FB tablet; 9. FC tablet.

The chromatogram profiles of tablets during manufacturing process: crude materials, extracts, granules and tablets using a-GF_{254} silica plate as a stationary phase and a mixture of n-hexane : ethyl acetate (4:1, v/v) as a mobile phase with vanillin as a spraying reagent can be seen in Figure 1.

The results of the chromatogram demonstrated that the chemical constituents in *cerme* leaves, from crude materials until tablets, were relatively unchanged. Tannins spot of purple color which was used as a marker (Rf 0.20 and 0.50) was identified in the extracts, extract powder, granules and tablets.

The tannins contents in crude materials, dry extracts, granules, and tablets were 2.97%, 15.33%, 10.63%, and 10.63% respectively. The content of tannins in the extract was found to be higher than that in crude materials due to a relatively long extraction process of active constitutents in the preparation of extracts. The addition of tablet excipients resulted in a decrease in tannins content. Tannins contents in granules and tablets did not differ significantly since tannins were resistant to heat and moisture. Thus wet granulation process did not reduce the content of tannins in the samples.

All formulae of A, B, and C showed good physical quality of tablets. However, formula A demonstrated a shorter disintegration time than those of formulae B and C. Thus it is expected that formula A will disintegrate

faster and be readily absorbed in the body so that it will exhibit a more rapid pharmacological effect than formulae B and C.

Conclusion

Cerme leaves extract could be formulated into a tablet dosage form which meets the requirements of physical quality of tablet. The addition of PVP K-30 as a binder at concentrations of 2, 3 and 4% may result in a tablet which meets the requirements. The selected formula was FA with PVP K-30 at a concentration of 2%.

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