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Formulation and Evaluation of Tablet From the Extract of *Persea Americana Mill.* for Nephrolithiasis

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Abstract : One of common kidney disease in Indonesia is nephrolithiasis or kidney stone. In the traditional systems of medicine, various type of plants and its species are used in the treatment of kidney stone. Avocado leaves (*Persea americana* Mill.)are the leaves of herbs that are useful to inhibit formation of calcium oxalate crystal in the rats' kidney. Objective of this study was to formulate a wet granulation method orally tablets of the vocado leaves (*Persea americana* Mill.) extract. All formulations met the requirements of the USP standard. Tablets were evaluated for weight variation, thickness, diameter of tablets, hardness, friability and disintegration time. The mass of the tablet in all formulas is has good flowability The difference in the amount of filler influence on hardness, friability and disintegration time of tablets. The friability increases with decreasing the concentration of Avicel PH101and disintegration time of three formulas decrease with increasing concentration Amprotab.
Keywords : Nephrolithiasis, *Persea americana* Mill, formulation, tablet.

Introduction

Nephrolithiasis, or kidney stone, is the presence of renal calculi caused by a disruption in the balance between solubility and precipitation of salts in the urinary tract and in the kidneys. A kidney stone is a multifactorial disorder resulting from the combined influence of epidemiological, biochemical and genetic risk factor [1,2]. In General, kidney stones are composed of calcium, uric acid stones, stone struvit and cystine stones. About 75% of kidney stone are composed of calcium oxalate crystal[3]. The prevalence and incidence of kidney stone are reported to be increasing across the world[4]. According to Indonesian Primary Health Research in 2013, one of common kidney disease in Indonesia is a kidney stone. In the fact, the prevalence of the disease is estimated at 7% in women and 13% in the male[5]. The formation of kidney stones is affected by intrinsic and extrinsic factors. Intrinsic factors i.e age, sex, and heredity, while extrinsic factors, i.e the geographical condition, climate, eating habits, a substance contained in the urine, jobs, and more[6].

The therapy in kidney stones is essential to remove stones, determine the type of stone, preventing damage nefron, control of infection, and reduce the obstruction. In comparison, there are alternative therapies are surgery through a conventional form of administering the drug and some step diet with certain medicinal plants[7].

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Indonesia has a great diversity of medicinal plants. The use of traditional medicines in Indonesia is part of national cultivation and has begun from centuries ago[8]. In the traditional systems of medicine, various type of plants and its species are used in the treatment of kidney stone. Avocado leaves (*Persea americana* Mill.) are the leaves of herbs that are useful for the various purpose of traditional medicine. The leaves have been used as a diuretic, anti-inflammation, anti-hypertension, hypoglycemia, diarrhea, sore throat, and bleeding[9]. In previous research, extract of avocado's leaves with ethanol extraction is an efficient agent to inhibit the formation of calcium oxalate crystal in the rats' kidney. The extract of avocado's leaves is a potential natural antioxidant and anti-inflammation compounds that able to prevent the formation of calcium oxalate crystal by interfering process of epithelial cell damage[10]. This research was to determine formulation and evaluation of the Avocado leaves (*Persea americana* Mill.) extract as a tablet dosage form that includes weight variation, thickness, the diameter of tablets, hardness, friability and disintegration time.

Experimental

Materials and Methods

Chemicals

The extract used in this study are the leaves of avocado (*Persea americana* Mill.) Collected from East Borneo. Aerosil, amprotab, avicel PH101, kollidon K-30, stearic acid were obtained from Merck (Germany). Ac-di-sol® were obtained from FMC Biopolymer (US).

Evaluating the Mixture of Powders and Granules

The main flowability properties of granules and powders (before compression) were characterized by drying shrinkage, true density, tapped density, bulk density, flow rate, the angle of repose, compressibility index (Carr's index).

Table 1. Tablets formula

Formula	A (%)	B (%)	C (%)
Extract	48,39	48,39	48,39
Aerosil	2	2	2
Avicel PH101	31,96	21,31	10,65
Amprotab	10,65	21,31	31,96
Kollidon K-30	2	2	2
Ac-di-sol (intra)	2	2	2
Asam stearate	1	1	1
Ac-di-sol (extra)	2	2	2

Table 2. Evaluation of powders and granules of each formula

	A	B	C
Drying shrinkage (%)	3,3	4,5	4,8
True density (g/ml)	0,462 ± 0,003	0,441 ± 0,003	0,439 ± 0,007
Tapped density (g/ml)	0,566 ± 0,009	0,503 ± 0,02	0,507 ± 0,018
Bulk density (g/ml)	1,467	1,497	1,47
Compressibility (%)	18,27 ± 0,837	12,18 ± 3,028	10,92 ± 3,683
Flow rate (g/detik)	11,77 ± 1,59	11,64 ± 0,987	11,02 ± 0,903
Angle of repose (°)	18,70 ± 0,819	21,11 ± 1,371	21,42 ± 0,342

Table 3. Evaluation each formula of the Tablets

	A	B	C
Weight variation (mg)	668,45 ± 17,31	664,21 ± 10,796	662,85 ± 9,727
Thickness (mm)	13,12 ± 0,018	13,16 ± 0,032	13,23 ± 0,013
Diameter of tablets (mm)	3,99 ± 0,077	4,16 ± 0,048	4,32 ± 0,082
Hardness (N)	60,01 ± 8,574	39,75 ± 11,805	27,38 ± 9,524
Friability(%)	0,071	0,279	0,49
Disintegration time (s)	417	273	104

Table 4. TLC of extract only and all formulas with extract

No	Rf	Observation			
		Visible	UV 254 nm	UV 366 nm	Vanillin sulphate
1	0,09	Orange	-	-	-
2	0,18	Orange	-	-	Orange
3	0,22	-	Purple	-	-
4	0,35	Yellow	-	-	-
5	0,52	-	Yellow	-	Purple
6	0,83	Yellow	Yellow	Red	Purple
7	0,95	-	-	-	Blue

Preparation of Tablets

All formula were preparation by wet granulation method. Ac-Di-Sol is added in the stage of wetting and drying (intragranular and extragranular) so the ability to break down and better deployment.

Evaluation of the Tablets

Weight Variation

Twenty tablets were randomly selected and weighed individually and the weights of tablets were compared with the calculated mean weight. In this method, not more than two tablets should have a deviation greater than pharmacopeia limits ± 5% of the weight.

Friability Test

Friability of the tablets was determined using friabilator. It subjected the tablets to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping a tablet at height of 6 inches in each revolution. The tablets were reweighed. Tablets were dedusted using a soft muslin cloth and reweighed. The percentage of the tablets friability was calculated. The desirable friability was determined as lower than 1%.

Diameter and Thickness

A vernier caliper was used to determine the thickness and diameter of randomly 10 selected tablets.

Hardness Test

The force required to break down a tablet in a compression is defined as the hardness or crushing strength of a tablet. In this study, ten tablets were randomly selected and individually placed in a hardness tester and then the hardness of tablets reported in N.

Disintegration studies on the tablets

Six tablets from each batch were utilized for disintegration studies in distilled water at 37˚C using a Disintegration Apparatus. The disintegration time was taken to be the time no granule of any tablet was left on the mesh of the apparatus.

Extract adjustment using thin layer chromatography (TLC)

Thin layer chromatography (TLC) was performed using silica gel GF254 plate, with a developer chloroform: ethyl acetate = 1: 1.

Result and Discussion

Evaluating the Mixture of Powders and Granules

This evaluation to know the nature of the granules to be compressed. The results of the evaluation of powders and granules of each formula can be seen in Table 2. Based on the test known that drying shrinkage between the tablet mass formula in the range of 3.3% to 4.8%, with the value of drying shrinkage, is expected mass of the tablet is not too wet and can be produced tablet is not crumbly. The value of a true density of 0.439 g/ml to 0.462 g/ml and tapped density demonstrate the value of 0.503 g/ml to 0.566 g/ml. Real density and tapped density depends on the shape and size of the particles. Compressibility calculations tablet masses ranging from 10.92% to 18.27%. This shows the flow ranges from free flowing to good flow according to Carr Index. The angle of repose tablet masses ranging 18,70º to 21,42º. This shows that the entire mass of the tablet has good flowability. From the flow rate, results all of the formula tablet mass was 11.02 g/sec to 11.77 g/sec. This value shows excellent flow properties so expect the printed mass does not cause problems at the time of filling into the tablet machine. Good flow is very important in the tableting process in order to produce the volume and weight of the tablet uniform.

In the tableting process, the machine used is set at 675 mg weight. Uniformity test results produced an average weight ranging from 662.85 to 668.45 mg. USP 27 states that the tablet should not deviate more than 5%, which means that the weight of each tablet should range between 641.25 to 708.75 mg. Thus these results have met the specified requirements. Weight difference can occur because the particle size and flowability of tablet mass. Examination of size uniformity test results produced an average diameter tablet ranged from 13.12 to 13.23 mm and thickness of tablet ranged from 3.99 to 4.32 mm.

In general, the tablets must be pretty hard to hold or not to break during packaging and shipping. In tableting process, tablet hardness was made uniform attempted to minimize the effect of violence against friability and disintegration time. From the results of the examination, testing tablet hardness ranged from 27.38 N to 60.01 N.

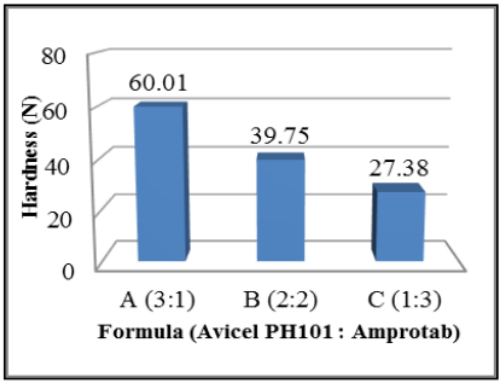

Figure 1. The average of the tablet hardness

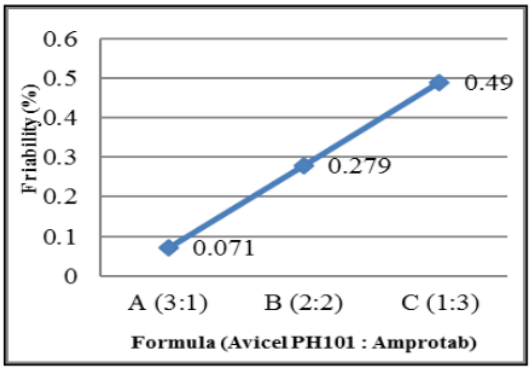

Figure 2. The effect of the concentration ratio between Avicel PH 101 with Amprotab against friability

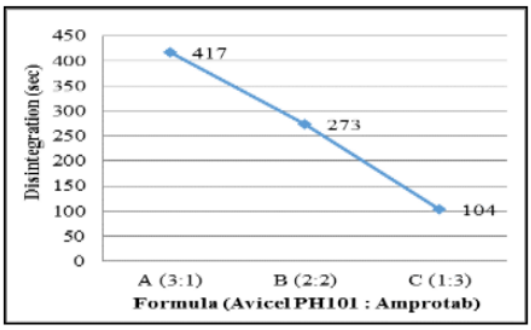

Figure 3. The effect of the concentration ratio between Avicel PH 101 with Amprotab against disintegration time

Test results of friability tablet ranged from 0.07% to 0.49%. All formulas in the requirements according to USP 27, which is still allowed to lose weight is up to 0.8%. Friability value relation to the increase in the concentration of Avicel PH101 can be seen in Figure 2. In figure 2, it is clear that the value of friability increases with decreasing the concentration of Avicel PH101. It can be concluded that the greater the concentration of Avicel PH101 friability value, the better resulting tablet compact and resistant to shock or damage in handling, packaging, and distribution.

Tablet disintegration time ranged from 104 seconds to 417 seconds. The value still in the requirements of the USP 27, disintegration time not more than 15 minutes (900 seconds). Relationship value disintegration time of each formula to the concentration compared with Amprotab and Avicel PH101 can be seen in Figure 3. From Figure 3 shows that the amount of filler, the disintegration time of three formulas decrease with increasing concentration Amprotab. For adjustment using TLC shown that the compounds contained in extracts of avocado leaves are still present in tablet dosage as the compound through the process of formulation.

Conclusion

The tablets of Avocado leaf extract can be made by a wet granulation method. All formulations met the requirements of the USP standard. The mass of the tablet in all formulas is had good flowability The difference in the amount of filler influence on hardness, friability and disintegration time of tablets. The friability increases with decreasing the concentration of Avicel PH101and disintegration time of three formulas decrease with increasing concentration Amprotab.

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