

TABLET FORMULATION FROM MENIRAN (*PHYLLANTHUS NIRURI* L.) EXTRACT WITH DIRECT COMPRESSION METHOD

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ABSTRACT

Objective: The aim of the present study was to obtain an optimized formula of meniran (*Phyllanthus niruri* L.) extract tablets that fulfilled the requirements as a good pharmaceutical preparation based on Indonesian Pharmacopoeia IV and USP XVII.

Methods: *P. niruri* plant was collected and determined at the Laboratory of Plant Taxonomy, Universitas Padjadjaran. First performed phytochemical screening to determine the content of secondary metabolites. Then designed five kinds of tablet formulas of *P. niruri* extract using a direct compressed method with a variation of concentration of filler. Each formula contains a similar concentration of *P. niruri* extract as the active ingredient, avicel PH 102 and amprotab with varying concentrations as filler, talcum, and magnesium stearate as a lubricant and Aerosil@200 vv as an adsorbent. Tablet print mass and quality of the resulting tablets were then evaluated. Also, check whether the resulting tablets still contain *P. niruri* extract as the active substance or not.

Results: The results of phytochemical screening of simplicia and viscous plant extract showed the presence of alkaloids, polyphenols, tannins, and flavonoids as secondary metabolites. The five formulas made contain avicel PH 102 and amprotab as binders and crushers and the expected results such as shape and durability as desired. The results of examination of shrinkage rate of mass drying of tablet prints from the above five formulas indicated an increase of value from formula A (5.4609 %) to formula E (5.8600%). This was because avicel PH 102 and amprotab had a considerable moisture content, so with the combination of both fillers could increase the water content from mass print tablets. Real density, compact density, and true density decreased from formula A to formula E. The amount of these densities were influenced by the shape and size of the particles. Flowability increased from formula A (23.7124°) to formula E (26.4210°) whereas compressibility increased from formula A (21.7222%) to formula E (29.4121%). Flowability and compressibility increase might be due to the uniformity of the particle size between the amprotabs and the other additives which could cause electrical charges to the print mass affecting the speed and flow of the print mass. All quality testing results including Weight (mg), Thickness (mm), Diameter (mm), Hardness (N), Friability (%) and Disintegration time (min.) had met the requirements. Thin Layer Chromatography showed that the resulting tablets still contain *P. niruri* extract as the active substance.

Conclusion: Overall results showed that the formulation fulfilled the requirements as a good pharmaceutical preparation based on Indonesian Pharmacopoeia IV and USP XVII.

Keywords: Meniran, *Phyllanthus niruri*, Directly compressed tablet, Formulation, Avicel PH102

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INTRODUCTION

Utilization of plants as medicinal ingredients has long been known by people in Indonesia commonly known by the name of jamu (herbal medicine) [1]. One type of plant that has not been developed completely but has many uses, especially in traditional medicine is meniran (*Phyllanthus niruri* L.). Meniran is a wild plant, a season that grows in a moist and rocky place [2]. It was reported containing alkaloids, balsams, sterols, carbohydrates, glycosides, flavonoids, tannins, saponins, phlobatannins, resins and terpene in trace; while the essential elements are detected Ca, Na, K, P, Mg, Mn, Fe, Cu, and Zn. the plant is rich in various chemicals that differ from people. In Indonesia, meniran is widely used for the treatment of diuretics, renal impairment, mouth ulcers, antipyretics, malaria, anti-diarrhoea, high blood pressure, menstrual cramps and bile disorders [4-6]. Choudhari *et al.* [7] developed a formula containing *Andrographis paniculata*, *Momardica charantia*, *Phyllanthus niruri*, *Terminalia chebula*, *Glycyrrhiza glabra* and *Punica granatum* for treatment and management of HIV-AIDS.

Based on the many benefits of meniran plants, one of them as anti diuretics, this article reports the formulation of the preparation of meniran extract in the form of tablets. If it is a tablet it will facilitate the use and transportation of the drug. Tablets are compact solid preparations, manufactured in a molded manner, in flat or circular tubes, either flat or convex surface, containing one or more drugs with or without additives. Additional substances used may serve as fillers, binders, lubricants, developing or crushing agents, or other suitable substances. Based on the method of making tablets can be

classified into two, namely tablet prints and directly compressed tablets [8, 9]. The tablets are made of medicinal materials and the fillers generally contain lactose and sucrose powder in various comparisons. The moist mass of the powder is pressed with low pressure into the molding hole. Then removed and allowed to dry. Tablet print is rather fragile, so be careful in packaging and distribution. On the other hand, the right-handed rock tablets have many advantages, especially in terms of durability and transportation. A direct compression method is a method of printing a medicinal substance or a mixture of medicinal substances and powdered auxiliary substances without going through the initial treatment process [10]. The direct compression method is the simplest method of making tablets compared with other tablet-making methods, wherein this method there are only two processes: mixing materials and printing. The thing to note in this method is the use of appropriate auxiliary materials for the manufacture of direct compression [11, 12]. Furthermore, making tablets from plant extracts is usually constrained so that many plant extract products are marketed in liquid or capsule form. So far, preparation of compressed tablets from meniran extract has never been reported.

MATERIALS AND METHODS

Material

Dried meniran extract (PT Phytochemindo Reksa), Dragendorff, Mayer reagent, Lieberman-Buchard reagent and avicel magnesium powder PH 102, amprotab, talcum, magnesium stearate, green dye (PT Kimia Farma) and Aerosil@ 200 vv (Degussa).

Equipment

Analytical Scales (Mettler Toledo), Electronic scales (Nagata), Tablet-printing machines (E. Korsch), Moisture determination balance (Ohaus), Tapped density meter, Hardness tester (Erweka type TB-24), Friability tester, time test device crushed tablets (Erweka ZT-2).

Methods

Collecting sample

Meniran plant (*P. niruri*) and its dry extract obtained from PT. Phytochemindo Mutual, Gunung Putri, Bogor, West Java which was then determined in the Laboratory of Plant Taxonomy Department of Biology Faculty of Mathematics and Natural Sciences Universitas Padjadjaran.

Phytochemical screening

The phytochemical screening of meniran was performed to determine the content of the secondary metabolite compounds of the alkaloids, flavonoids, polyphenols, tannins, monoterpenoids, sesquiterpenoids, steroids, triterpenoids, quinones and saponins contained in the *P. niruri* simplicia by modification of the method of Farnsworth [13]

Formulation and making meniran extract tablets

The formulation of directly compressed tablets were designed with reference to existing libraries [12, 14]. Made five kinds of tablet formulas extract meniran using direct compression method with variations of concentration of filler. The formula was a formula for one tablet so that this meniran extract tablet had a theoretical weight of 600 mg. In each laying process, we weighed a formula for 150 tablets. The steps taken in the process of making extract meniran tablets were as follows: first, all the tablet material sieved weighed and mixed until homogeneous. This homogeneous mass was then printed into a tablet using the E. Korsch tablet machine with punch 12.

Tablet print mass testing

Tablet mass testing included drying drift, flowability, real density, compact density, true density, and compressibility. The procedure of determining these tests was based on Aulton method [15]. Loss of drying was analyzed using a drying shrinkage measuring tool, Moisture determination balance (Ohaus). Flowability was determined as follows, the tablet mass was placed in the funnel of the flow rate test vessel whose bottom was closed. The printed mass coming out of the apparatus was calculated in the flow velocity by

calculating the time required by the amount of powder to descend through the test tool funnel by using the stopwatch from the beginning of the lower cap opening until all the granular mass flows out of the test apparatus. The granule deposits can be used to calculate the resting angle (flowability). Real density was determined by using pycnometers and liquids that did not dissolve granules ie liquid paraffin whereas true and compact densities were determined using measuring glass. Compressibility was calculated based on Carr index (compact density-real density)/compact density x 100%).

Tablet quality testing

Tablet quality testing includes weight uniformity, uniformity size, hardness, crispness and crumbling time. Weight uniformity test was based on Indonesian Pharmacopea III [8], uniformity size based on Indonesian Pharmacopea IV [9], Hardness was determined using Hardness tester. Friability was determined by friability tester in which tablets were weighed by approximately six point five grams, then incorporated into the tablet rigidity testers. The tool runs for four minutes at twenty-five lap speeds per minute. Tablets were still intact weighed, then calculated to lose weight. The weight loss allowed was not more than 0.8% USP XXVII [22].

Qualitative test of tablet preparation with thin layer chromatography

For thin layer chromatography, silica plate GF γ 254 γ was used with n-butanol, acetic acid and distilled water (4: 1: 5) as well as UV-254, UV366 nm and ammonia vapors.

RESULTS AND DISCUSSION

Plant determination

Determination conducted at the Laboratory of Taxonomy, Department of Biology Faculty of Mathematics and Natural Sciences University of Padjadjaran showed that the plants used in this formulation were meniran (*Phyllanthus niruri* L.) plants.

Phytochemical screening

The results of phytochemical screening of simplicia and viscous extract of *P. niruri* showed several classes of secondary metabolite compounds as seen in table 1. Nakweti *et. al* [16] mentioning that they found saponins in their Congo's *P. niruri* sample. Masruroh *et. al* [17], however, found saponin in their sample. Alegantina [18] reported that they found alkaloids, flavonoids, phenols, coumarins, tannins, terpenoids, and lignans (phyllanthin and hypophyllanthin). This difference in phytochemical screening results was most likely due to the different origin of the plant being examined.

Table 1: Phytochemical screening of simplicia and meniran viscous extract

Secondary metabolite	Simplicia	Viscous extract
Alkaloids	+	+
Polyphenols	+	+
Tannin	+	+
Flavonoids	+	+
Mono and Sesquiterpene	-	-
Steroids and Terpenoids	-	-
Quinone	-	-
Saponins	-	-

Notes: +: detected,-: not detected

Formulation of meniran extract tablet

The formulation of the extracted tablets was designed as shown in table 2. The production of tablets was divided into two, by granulation and direct compression methods. Meeus [18] reported differences from both methods. Suhery *et. al* [20] in their experiments stated that the results obtained showed that both methods produced the physical properties of a good tablet. However, the method of direct compression provides a disintegrating faster than with the wet granulation method. They

applied statistical test using independent sampling ($P < 0.05$) between the formula and the method of direct compression and wet granulation. Reiza [21] in his study on the comparison of the use of the wet and dry granulation method to the stability of the paracetamol active substance stated that on the use of dry granulation method in the direct compression method produced tablets that had better stability than tablets of wet granulation method. This possibly due to the process of wet granulation, paracetamol in the presence of water would be hydrolyzed to acetic acid and p-aminophenol.

Table 2: Meniran extract tablets formula

Formula	A (%)	B (%)	C (%)	D (%)	E (%)
Dried meniran extract	44.67	44.67	44.67	44.67	44.67
Avicel PH 102	50.73	47.50	45.00	42.50	40.00
Amprotab	-	3.23	5.73	8.23	10.73
Talcum	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	2.00	2.00	2.00	2.00	2.00
Aerosil@200 vv	0.50	0.50	0.50	0.50	0.50
Colouring substance	0.10	0.10	0.10	0.10	0.10

Notes: A, B, C, D, E: type of formula

On the determination of the formula of this meniran extract tablet, it was used avicel PH 102 and combined with the amprotab as filler, so it could form the size of the tablet as desired. The choice of avicel PH 102 was due to having a larger particle size compared to avicel PH 101, so the resulting flowing power was better than avicel PH 101 which had smaller particle size. In addition, avicel PH 102 was also widely used as a filler on the manufacture of tablets that use the method of direct compression. The use of avicel PH 102 on each tablet formula was a variation of five concentrations, i. e 40%, 42,5%, 45%, 47,5% and 50,73% in order to see avicel PH 102 effect on tablet preparation, avicel PH 102 could also act as a binder and crush in tablet formulations. In addition, a combination of Avicel PH 102 and amprotab was also made, which aimed to see the effect of the combination on the tablet preparations. In the manufacture of direct compression tablets, avicel PH102 is needed as a binder in the absence of granulation process.

As a lubricant in the formula of this meniran extract tablet was used talcum and magnesium stearate. The use of these two lubricants simultaneously was intended to provide a good lubricant effect on tablet formulas, which, as we had seen, had both advantages differed from one another. Talcum with a concentration of 1-5% could give good anti-adherent and glidant effect but had poor lubricant effect, while magnesium stearate with concentration 0,25-5% could have good lubricant effect but had less anti-adherent and glidant effect good. It was hoped that by combining the two lubricants could increase the mass flow of tablet prints upon entering the tablet

mold, it could prevent the sticking of the print mass of tablets on punch and die and could make the dosage more glossy, thus increasing the aesthetic value of the tablet itself.

The result of a mass print of tablet extract meniran

Testing the print mass of the tablet was done before the tablet tableting process takes place. This test was intended to determine whether or not the print mass was printed into tablets, so this test could be used as a supporting factor to determine the quality of tablets to be printed. There were several requirements that must be met for the printing mass of the tablet to be printed properly, including drying shrinkage test, flowability, real density, compact density, true density and compressibility [8]. The results of tablet mass testing of each formula can be seen in table 3.

The results of examination of shrinkage rate of mass drying of tablet prints from the above five formulas indicated an increase of value from formula A to formula B. This was because avicel PH 102 and amprotab had a considerable moisture content, so with the combination of both fillers could increase the water content from mass print tablets, so automatically the shrinkage rate of mass drying tablets print would increase as well. With the specified water content was expected to mass print tablets would not be too wet so that the mass of tablets prints could be hammered well into dosage tablets. In addition, the mass print tablets should not be too dry because the tablets would become brittle and could remove the binding capacity of the print mass that tends to form capping and lamination.

Table 3 Result of meniran mass testing print tablet

Formula	A	B	C	D	E
Testing					
Loss on Drying (%)	5.4609	5.8602	5.6497	5.6499	5.6800
Real density (g/ml)	0.6524	0.5323	0.5139	0.5070	0.5190
Compact density (g/ml)	0.8334	0.6947	0.7146	0.7215	0.7353
True density (g/ml)	1.6151	1,5236	1.4874	1.4773	1.4445
Flowability (°)	23.7124	26.2969	24.0748	24.8435	26.4210
Compressibility (%)	21.7222	23.3818	28.0763	29,7210	29,4121

Notes: A, B, C, D, E: type of formula

The amount of real density and incompressibility density was influenced by the shape and size of the particles. The density of spherical particles or spheres would be greater when compared to needle-shaped particles and stems. While the particle size was larger, it had a larger particle density value compared to small particles. Real density and compact density tests were performed to determine the compressibility of the print mass of tablets.

Tablet flowability testing was done without vibration. From the results of testing the flow power, the addition of amprotab into the formula could decrease the mass flow of print. This was due to the uniformity of the particle size between the amprotabs and the other additives which could cause electrical charges to the print mass affecting the speed and flow of the print mass.

The result of quality testing of meniran extract tablet

It is necessary to perform a quality test on tablets that have been produced. Testing the quality of the tablet includes uniformity of

weight, uniformity of size, hardness, friability and crushed time [8, 9]. The results of these tests can be seen in table 4. The results of testing the quality of tablets above showed that uniformity of weight, uniformity of size, friability and the crushed time of the five tablet formulas had met the requirements of Indonesian Pharmacopoeia IV [9] and USP XXVII [22].

Tablet size uniformity

The results of the uniformity test of the size indicate that the average thickness and diameter of the tablet meet the requirements of Indonesian Pharmacopoeia IV [9] where it was stated that the tablet diameter was not more than three times and not less than one-third of the thickness of the tablet (table 4).

Tablet weight uniformity

The charging volume used in this tablet printing process was set to a weight of 600 mg by adjusting the bottom punch. Indonesian

Pharmacopoeia III [8] stated that tablets weighing more than 300 mg should not deviate more than five percent, meaning that the

weight of each tablet should be between 570 mg to 630 mg. Thus the results of the study as listed in table 4 established requirements.

Table 4: Quality testing result of meniran extract tablet

Formula Testing	A	B	C	D	E
Weight (mg)	601.4550±4.3182	604.0400±6.7348	606.8850±7.9118	605.6250±8.5739	601.7200±5.5539
Thickness (mm)	5.4015±0.0105	5.3415±0.0589	5.4215±0.0222	5.1060±0.0466	5.2930±0.0761
Diameter (mm)	12.1420±0.0068	12.0995±0.0462	12.1190±0.0479	12.0825±0.0405	12.1165±0.0299
Hardness (N)	116.4500±7.5612	112.5000±8.3291	106.4250±6.3013	109.9250±7.6129	107.8750±7.6336
Friability (%)	0.1579±0.0419	0.2642±0.0156	0.3522±0.0314	0.4544±0.0346	0.5881±0.0801
Disintegration time (min.)	02.20	02.35	04.12	05.45	07.10

Notes: A, B, C, D, E: types of formula

Tablet hardness

From the results of hardness tablet testing using Erweka machine, the resulting average hardness ranging between 106-116 N. Hardness tablets were attempted to have a small range and made uniform, this was intended to minimize the influence of violence against time devastation and friability, so that the time difference was destroyed and the friability between one formula with the other could be regarded as the effect of different filler concentrations [8, 9].

Friability

From the results of testing the quality of tablets, the resulting average friability ranged from 0.1579-0.5881. This value had met the requirements in accordance with USP XXVII [22], i. e the allowable weight loss was up to 0.8%. It was found that the greater the concentration of avicel PH 102, the value of friability become decreased, this indicated that the greater the concentration of avicel PH 102, the resulting tablet was better and not fragile. This was possibly due to avicel PH 102 had properties that made the tablet became not easily broken and hold scraping.

Tablet disintegration time

The disintegration timing test of the five tablet formulas of this meniran extract found that with the increase of the avicel concentration of PH 102 in the formula could speed up the disintegration time of the tablets preparations. This was due to avicel PH 102 itself was as a destroyer or disintegrant. The crushed time of these five formulas ranges from two to seven and a half minutes. The value still meets the requirements stipulated in the Indonesian Pharmacopoeia IV [9], that was the time of disintegration should not be more than fifteen minutes.

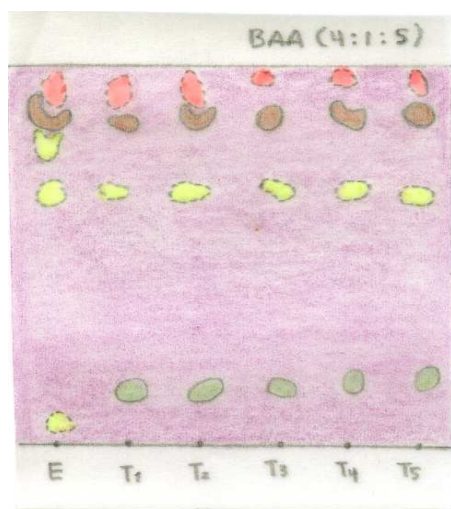


Fig. 1: Thin layer chromatography results from extracts and meniran tablets, Notes: E (Ekstrak meniran), T₁ (Formula A), T₂ (Formula B), T₃ (Formula C), T₄ (Formula D) and T₅ (Formula E)

Qualitative test of meniran extract tablet

Qualitative test was performed on extract and fifth formulas of meniran extract tablets using thin layer chromatography (TLC) method. This test aimed to be able to identify the uniformity of the compound content contained in meniran thick extract and the five formulas of meniran extract tablets. This was indicated by spots that have the same R_f value. It was also intended to identify the compounds of quercetin and nirurin, which were thought to have a diuretic effect [23]. The stationary phase of TLC was silica gel GF254 plate, the eluent was n-butanol: acetate: water (4:1:5) and spotting viewer was UV 254 and 366 nm, and ammonia vapor. Chromatographic results can be seen in the fig. 1.

Statistical analysis

The statistical analysis was guided by Sudjana [24]. From the result of data analysis using Perfect Random Design, with 95% confidence gave result F_{count} bigger than F table (43,4934>3,48). This indicated that the five variations in avicel concentration of PH 102 had the significantly different effect on tablet disintegration time. At the concentration of avicel PH 102 40% gave the mean of the longest destroyed time of 7.27 min, while at concentration avicel PH 102 50,73% gave mean of fastest crushed time that is 1,92 minute. To find out which concentration was most influential to tablet disintegration time than Newman-Keuls test was carried out. Newman-Keuls test results showed that not all treatments give significant difference ($\alpha = 0.05$), there was a difference between the formulas 5 and 2, 5 and 1, 4 and 2, 4 and 1, 3 and 1. From these results it was concluded that the concentration of avicel PH 102 40% gave significant difference with avicel concentration of PH 102 47,5%, avicel concentration of PH 102 40% gave significant difference with avicel concentration PH 102 50,73%, avicel concentration of PH 102 42,5% gave significant difference with avicel concentration of PH 102 47,5%, avicel concentration of PH 102 42,5% gave significant difference with avicel concentration of PH 102 50,73%, avicel concentration of PH 102 45% gave significant difference with avicel PH concentration 102 50.73%. While the other comparison did not make a significant difference.

Preparation of tablets directly compressed tablet from the meniran extract has not yet investigated, but the tendency to make tablets from plant extracts that efficacy must be recognized has begun many in the interest of researchers. Duraisankar and Ravichandran [25] stated that the antipyretic effect of the aqueous extract of polyherbal (*Sweetia chirata*, *Solanum xanthocarpum*, *Tinospora cortifolia*, *Operculina turpethum*, *Cyperus rotundus*, *picrorrhiza curroa*, *Melia azadirachta*) was comparable to that of paracetamol (150 mg kg⁻¹ body weight p. o), a standard antipyretic agent. Muthiah [26], for example, reportedly prepared a chewed tablet formulation of dewandaru leaf extract (*Eugenia uniflora* L.) with a combination of mannitol-lactose filler. Dewandaru leaves are said to be efficacious as antibacterial, anti-free radical, and anti-diarrhea. Preparation of tablets from tapak dara leaf extract that is thought to be efficacious as an anti-cancer drug because it contains vinblastine alkaloids and vincristine has been studied as a result of thesis [27]. Hussein [28] claimed have made a novel retardant by formulating sustained release tablet of Pentoxifylline using Okra (*Abelmoschus esculentus*)

extract. One of the researchers [29] has also been used direct compression method for the manufacture of tablets from *Andrographis paniculata* leaf extract but this researcher uses a different formula. On the other hand, a wet granulation method for making tablets from plant extracts has also been reported [30].

CONCLUSION

Based on the results of research that has been done, it can be concluded that the *P. nirusi* extract as one of the natural ingredients diuretic can be made into a tablet that meets the requirements as a pharmaceutical preparation. Based on the results of the print mass testing and the quality of the tablets that have been performed, the tablets have uniformity, size, hardness, friability and crushed time meets the requirements set forth in the Indonesian Pharmacopoeia IV and USP XXVII. It is found that the greater the concentration of avicel PH 102 will decrease the value of friability tablets, but also the greater the concentration of avicel PH 102 will speed up the destruction time of the tablet. It is also found based on the results of qualitative tests using thin layer chromatography that the nutritious substances extract is still present in the tablets after going through the stages of formulation.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

No conflict of interests between authors

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