Study of Tablet Formulations Containing a Combination of Secang (*Caesalpinia sappan* L) and Gambir (Uncaria Gambir Hunter Roxb) Extracts as Uric Acid Lowering Agents

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Abstract. The number of people with hyperuricemia tends to increase in line with the growth in the level of community welfare. The proportional combination of secang and gambir extract (formula extract = FE) was proven to be able to reduce blood uric acid levels with an effective dose of 75 mg/kg bw (body weight) in hyperuricemia rats. This study aimed to design FE into the final dosage form of tablets. The drying process of each semisolid extract was carried out using five types of fillers (dextrin, maltodextrin, cornstarch, lactose and amprotab) with a ratio of 1:1 to 1:3 of each extract and filler using a vacuum oven. The designed extract powder of secang and gambir was accessed based on the following parameters: water content, angle of repose degree, and total phenol content. The selected of each powder extract was prepared using a ratio of 1:1 extract to corn starch for secang and a 1:1 ratio (extract: amprotab) for gambir powder extract. FE was prepared by combining the proportional amounts of the selected secang and gambir powder. Furthermore, the tablet formulation of FE was composed by the direct compression (DC) method using different disintegrants, namely, amprotab (Formula A) and explotab (Formula B). Evaluation of both granulated masses demonstrated that all parameters complied with the requirement. Furthermore, evaluation of the final tablet physical properties revealed that formulation with 8% explotab as a disintegrant agent performed better than formulation with 8% amprotab. Tablet properties of Formula B fulfilled the pharmacopeia requirements, namely, mean weight 767.0 ± 17.8 (mg), hardness 4.01–6.60 (kg/cm^2), friability 0.7 (%), and disintegration time 13.0–15.0 (min).

Keywords: Gambir · secang · uric acid-lowering formula extract · tablet dosage form · direct compression

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1 Introduction

Secang and gambir are medicinal plants commonly used by the local people to treat disease symptoms. Previous research demonstrated that the proportionated combination of these two plant-derived extracts exhibited anti-hyperuricemia. The in vitro study demonstrated that this combination had the inhibitory activity of xanthin oxidase higher than gambir extract and the scavenging radical activity was almost similar to both single extract [1]. Furthermore, the in vivo evaluation exhibited that this combination given to hyperuricemia rat models at a dose of 75 mg/kg bw orally for 28 days could decrease blood uric acid as much as 30–40% compared to the hyperuricemia control group. ($p < 0.05$) [1].

It was generally that the extract obtained from organic extraction physically formed a thick semisolid mass, oleoresin-rich, rubbery-like, and sticky extract. It was a consequence that this extract had a tendency to be less homogeneous and difficult to process into the final dosage form, hence the efforts to convert the extracts into dry powder mass were a necessity. In the powder form with controlled moisture, the plant-derived extract had several advantages, such as being more practical in drug preparation, accurate in the dosage calculation, ensuring quality during storage, and minimizing costs in transportation [2].

The drying process with the addition of any kind of carriers or fillers could shorten the time and at lower temperature processing so that protected the compound of extract from the heat damage [3, 4]. Some factors should be an evaluation before defining the type of carrier including physical and chemical compatibility, particle size distribution, flowability, compressibility/compactibility, and solubility that could influence the stability of dry material [5]. Lactose, maltodextrin, dextrin, starch, and other fillers are commonly employed in the drying of semisolid extracts that are chosen based on the purpose of the further product formulation. It is commonly for the dry form of plant-derived extracts to be slightly hygroscopic. Furthermore, the DC technique is an appropriate approach for tablet formulation [6]. The dry granulation procedure was carried out utilizing the suitable excipients to produce a granulated mass that was in accordance with pharmaceutic criteria. These studies aimed to formulate a tablet dosage form containing a proportional combination of secang and gambir extracts that fulfilled pharmaceutical requirements and were of high quality. A drying optimization of each extract was previously performed to acquire the dried-selected extracts that comply with the standard. The results showed that the FE tablet composed using explotab as a disintegrant delivered a final product that fulfilled pharmacopeia requirements.

2 Materials and Methods

2.1 Materials

Gambir (twigs and leaves) were obtained from Halaban Village, Kabupaten Lima Puluh Kota, West Sumatra Province (−0.3383816795103576, 100.7457693247152). Previously, it was determined at the Center for Biology Research-LIPI Cibinong. Secang was obtained from the Center for Research and Development of Medicinal Plants and Traditional Medicine (B2P2TOOT) Tawangmangu in the powder form. Chemicals for analysis and formulations were pro-analysis and pharmaceutical grade.

Table 1. The amount of TS30 extract and filler on each proportion

No	Ratio TS30:filler	TS30 (g)	Filler (g)
1	1:1	100/30 x ½ x 10 = 16.66	½ x 10 = 5.00
2	1:2	100/30 x 1/3 x 10 = 11.1	1/3 x 10 = 3.33
3	1:3	100/30 x 1/4 x 10 = 8.32	1/4 x 10 = 2.50

2.2 Extraction

Fresh gambir was dried in an oven at 50 °C and pulverized into a fine powder using a grinding machine. Extractions of secang and gambir were conducted using maceration at room temperature. The amount of 250 mg secang powder was macerated with 1000 mL ethanol for 14–18 h with agitation. After being separation using filter paper, the mass was re-extracted using a half of the original eluent volume. Furthermore, the filtrate was collected and evaporated using vacuum evaporator until semisolid mass obtained. Extraction gambir powder was conducted using the similar process above. The characterizations of the semisolid extract obtained, which included organoleptic, loss on drying, water-soluble and alcohol-soluble ingredients, and total phenol, were carried out based on the BPOM's extract quality standards [7]. The extract gained was stored in a closed bottle for further research.

2.3 Drying Extract

Each secang or gambir powder extract is made by weighing the each TS30 semisolid extract and filler (lactose, dextrin, amprotab, corn starch, and maltodextrin) in the following ratios: 1:1, 1:2, and 1:3 (Table 1). The TS30 extract was prepared by adding a certain amount of alcohol to extract calculated according to the following equation.

$$TS\_final = \frac{TS\_initial}{(1 + x)} \tag{1}$$

From the formula, TS = total solid, X (mL) = volume of alcohol added, TS-initial = determined gravimetrically. After being mixed homogeneously, the mixture was dried in a vacuum oven at 50 °C for 12 h. The solid mass obtained was sieved to a certain size and the powder was stored in an airtight container. Each extract powder produced was evaluated on some parameters, including the angle of repose [8], water content (Karl Fisher method), and total phenol using the Folin Ciocalteu reagent [9].

The weight of powder extract that was prepared was 10 g.

2.4 Preparation Formula Extract (FE)

Formula Extract (FE) powder was prepared by mixing the selected gambir and secang extract dried powder with a proportionate composition homogeneously. Analysis of the FE powder was carried out firstly with the parameters of the angle of repose, water content, and total phenol content similar to the methods above before being compacted.

Table 2. Tablet formulation

Ingredients	Formula A	Formula B
Active material: FE powder	67%	67%
Filler: Laktosa alfa-monohidrat	20%	20%
Adhesive: Avicel PHMCC	2%	2%
Disintegrant: Amprotab	8%	–
Disintegrant: Explotab	–	8%
Glidant: Mg Stearate	2%	2%
Antiaderent: Talk	1%	1%
Total	100%	100%

2.5 Tablet Formulation

Tablet preparation was carried out by the direct compressing method and dry granulation based on previous literature [10, 11]. There were two tablet compositions that were prepared using different disintegrant materials (Table 2).

The FE tablet regimen dose was designed to be 1–2 tablets, twice daily. It was based on the conversion of the effective animal dose (semisolid FE) to the human dose, namely 75 mg/kg bw (rat), which was equal to 840 mg/70 bw (human). The corresponding dose of the selected FE powder was blended with the excipients by the trituration method for 12 min. Then, a given amount of glidant and antiadherent materials were added and remixed for 4 min until a homogeneous mass was obtained. The granule properties were analyzed based on a previous study [8] which included moisture content, compressibility, and flow rate. The powders were compacted in a manual tablet machine with a final tablet weight of approximately 780 mg. In addition, based on previous research, the physical characteristics of tablets such as weight uniformity, tablet hardness, tablet friability, and disintegration time were investigated [8].

2.6 Data Analysis

The experimental results were expressed as the Mean ± SEM. The data were analyzed statistically using t-test using the SPSS13 program. A p-value of less than 0.05 was considered statistically significant.

Table 3. Semisolid extract characterizations

No	Parameter tested	Secang extract ($x \pm sd$)	Gambir extract ($x \pm sd$)
1	Yield of extraction (%)	6	19
2	Water content (%)	5.15	7.5
3	Organoleptic	Semisolid mass, dark red color, distinctive odor, bitter taste	Semisolid mass, dark brown color, distinctive odor, bitter taste
4	Loss on drying (%)	47.86 ± 0.22	38.34 ± 1.84
5	Water-soluble contend (%)	7.50 ± 0.46	5.15 ± 0.07
6	Alcohol-soluble content (%)	8.50 ± 0.25	10.49 ± 0.39
7	Fungus/yeast contaminant (colony/g)	$< 10^{-4}$	$< 10^{-4}$
8	Heavy metal (As, Cd, PB, Hg)	n.d.	n.d.

3 Results

3.1 Extraction

The row materials (secang and gambir) were extracted separately and produced a rubber-like mass, respectively. The semisolid extract of gambir was green, while the extract of secang was slightly reddish. Gambir extract had a higher yield than the other because it was derived from leaves and twigs that contained chlorophyl and fat. The yield of the extraction and semisolid extract characterization were depicted in Table 3.

Values were averaged in triplicate. N.d. = not detected.

3.2 Extract Powder

The drying process revealed that all compositions of semisolid extracts and the type of filler used resulted in the mass of the extract powder. Except the secang extract that was made using a 1:1 (extract:amprotab filler) ratio produced a sticky mass. The angle of repose and water content values of each secang and gambir dry powder extract qualified the requirements. Furthermore, the results of the total phenol content varied, and the addition of filler had a tendency to decrease the total phenol content. The dry powder extracts of secang and gambir for each composition and type of filler used with all parameters tested were presented in Table 4.

Table 4. Dry-powder extract characterizations

No	Pengisi	Ratio FE: filler	Secang powder			Gambir powder		
			Angel of repose (°)	Water content (%)	Total phenols (%)	Angel of repose (°)	Water content (%)	Total phenols (%)
1	Lactose	1:1	18.77	5.35	20.97	18.77	5.35	18,23
		1:2	17.70	5.18	18.05	17.70	5.18	14,69
		1:3	18.12	5.00	12.92	18.12	5.00	11,43
2	Dextrin	1:1	18.25	6.08	18.11	19.14	3.47	18,16
		1:2	2.74	1.17	10.38	18.43	3.35	12,03
		1:3	4.73	1.53	5.00	10.48	2.98	8,17
3	Amprotab	1:1	-*	-*	-*	2.47	3.87	18,62
		1:2	9.80	2.26	13.91	8.33	2.28	13,78
		1:3	12.71	4.93	10.54	5.66	2.95	9,63
4	Corn starch	1:1	13.95	6.18	28.21	15.43	4.38	17,63
		1:2	18.43	3.59	12.22	18.54	5.36	13,31
		1:3	9.82	3.11	10.29	11.44	6.71	9,33
5	Maltodexstrin	1:1	15.86	5.95	21.58	11.31	3.80	18,16
		1:2	16.32	5.33	17.06	17.35	5.22	12,52
		1:3	12.38	5.35	11.86	10.28	3.90	9,41

* Sticky

3.3 Tablet Characterization

The final tablet dosage form of FE was prepared by DC and dry granulation method with a targeted tablet weight of about 780 mg. The analysis result of granulated mass demonstrated that both tablet formula satisfied the pharmaceutical requirement (water content, flow rate, angle of repose dan compressibility test). However, examination of the finished tablet revealed that formula B, which contained explotab as a disintegrant, performed better in terms of disintegrant time. Formula B wass also more resistant to brittleness and has an average tablet weight that was closer to the intended tablet weight. The performance of the granulated mass and the final tablets of each formula developed were presented in Table 5 and Table 6.

Table 5. Physco analysis of the granulated mass

Parameter tested	Formula		Requirement
	A (Amprotab)	B (Explotab)	
Water content (%)	4,0	4.6	2–5
Flow rate (g/second)	0,8	2.5	< 10
Angle of repose (^{0})	23,1	18.7	< 25
Compressibility test (%)	20	22.9	< 21

Table 6. Physco analysis of the tablet dosage form

Parameter tested	Formula		Requirement
	A (Amprotab)	B (Explotab)	
Mean weight (mg)	738,0 ± 12,1	767,0 ± 17,8	
Hardness (kg/cm^2)	3,5–5,4	4,01–6,60	4–8
Friability (%)	5,1	0,7	0,5–1
Disintegration time (min)	21,0–25,0	13,0–15,0	< 15

4 Discussion

The trend of medicinal plant usage among the local people is increasing. The efforts to design dosage form formulations that are more patient-acceptable without affecting the quality of the final product were important. The final natural product preparation often comprises a high concentration of active ingredients and has a hygroscopic property that makes it highly unstable. As a result, suitable excipients and/or the application of appropriate processing methods are required prior to tablet compression [6].

Extract preparation in this study was carried out by maceration using ethanol and water as solvents. The selection of the two types of solvents with reference to the regulations from BPOM [12] and the extraction process is relatively safer than the use of other solvents. The results of extraction of each raw material were showed in Table 3 that the water content of both semi solid extract was less than 10% that these values complied with BPOM's standard extract quality [7]. The levels of hazardous heavy metal (Pb, Cd, As and Hg) were also fulfilling the BPOM's requirements. The limits of required heavy metal content in the natural product is standardly less than 10 ppm (Pb), 0.3 ppm (Cd), 5.0 ppm (As), and 0.5 ppm (Hg). Furthermore, analysis of microbiological revealed that the level of yeast/mold contained in both extracts was less than 10^{-4} colonies/gram and this suggested that those values appropriated with microbiology requirement [7].

The dry powder extracts of secang and gambir for each composition and type of filler used were presented in Table 4. It was shown that the angle of repose and water content value of each dry powder extract of secang and gambir qualified the requirements

(less than 10%). It was stated that the lower the water content, the better the quality of the natural product due to prevent for microorganism growth and chemical alterations during dried storage [13]. The angle of repose value of all powders exhibited less than 25^0. Powder flowability has generally been described by the angle of repose. Previous studies had classified this property in the following order, excellent (<25), good (25–30), fair (30–40), and > 41 poor (14). Referring to the criteria stated above, these results exhibited that all dry powder extracts produced with the composition and type of filler materials used were presented dried-powder extracts with good flowability. However, the composition of a 1:1 (secangTS30:amprotab) ratio presented a sticky mass that gave consequence the determination of its physico-mechanical properties impossible. Furthermore, the total phenol content was used to determine the kind of selected secang and gambir extract powder.

Phenolic substances have an aromatic ring, a hydrogen atom of the phenolic hydroxyl group, and are known to be powerful natural antioxidants. These compounds proven exhibiting a key role in wide range of biological and pharmacological properties such as anti-inflammatory, anticancer, antimicrobial, antiallergic, antiviral, antithrombotic, hepatoprotective, food additive, signaling molecules [15]. As a result of these considerations, the level of total phenol was stated as one of the parameters examined. The dry extract of secang with the greatest total phenol concentration was prepared using a 1:1 corn starch filler, with a total phenol level of 28.21%. Meanwhile, the use of lactose in a 1:1, 1:2 and 1:3 (TS30:filler) ratio in drying gambir extract yielded the total phenol concentration with similar value, which was each 18,62%. So that for powdered extract of gambir, a ratio of 1:1 (TS30:amprotab) was chosen as the selected dry powder. The selection of gambir extract powder is based on the use of the least quantity of filler capable of providing the maximum total phenol content. The extract content in each selected dry powder was around 50%. Furthermore, the both selected-dried powders extracts were mixed in the proportional combination (called FE) that is equivalent to the effective dose of the semisolid formula extract in the lowering uric acid activity (equal to 75 mg/kg bw on a hyperuricemia rat model) (data not shown). The addition of carrier in the drying process of a semisolid extract had some advantageous such as to coat the flavor components, raise the total solid amount, speed of the drying time, protect materials from head damage and the dry extract form more standardized and qualified [16, 17].

It was generally that natural final product consisted high volume of active extract ingredient. The dry extract powder has hygroscopic properties and tends to be sticky. The suitable tablet processing was conducted by a direct compressing and dry granulation method. The use of a dry granulation process is preferable to wet granulation. The wet approach may result in the active substances to become moister. In addition, wet granulation is generally carried out using a binder excipient that increase the tablet hardness and consequently prolonged disintegration time.

In the tablet formulation (Table 2), lactose monohydrate was used as filler with the consideration that this excipient had good flow properties. This advantage can compensate for the active components' tendency to be hygroscopic and agglomerate. Lactose monohydrate contains one water molecule that is equivalent to 5% crystalline water [18]. In DC, lactose is routinely combined with Avicel to enhance disintegration time

(6). Avicel or Microcrystalline cellulose is a fine powder compound that prepared by acid hydrolysis of cellulose using acid [19]. This compound is one of the most widely used filler-binders for DC because of its excellent compressibility and disintegrant properties [20, 21]. The percent of avicel as a binder in tablet formulations was in a small amount, just around 2%. This material, in addition to serving as a binder, was expected to increase the performance of the final tablet. However, avicel has a disadvantage in that its flow qualities are slight poor, hence it is frequently mixed with other fillers to improve these properties [22]. Due to its extremely low coefficient of friction and residual die wall pressure, this compound is a self-disintegrating material with a low lubricant requirement. These characters, however, these characteristics impose the use of disintegrants and lubricants in the design formulation. Avicel and super-disintegrants may, in fact, collaborate to promote rapid disintegration. Avicel also has a wide API (active pharmaceutical ingredient) compatibility, physiological inertness, and ease of handling [19, 23–28]. It is not recommended to use avicel in levels more than 20% of the active ingredient both as single or in combination with other excipients, such as lactose and starch [18].

There were 2 types of tablet formulas developed (Table 2), formula A and formula B, which used different disintegrant compounds, namely amprotab and explotab, respectively. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release, mainly with high drug concentrations [29]. In tablet formulation technology, the disintegrant agent is one type of additive compound that plays an important role in the physical properties of the tablet. The use of a combination of excipients in tablet formulation affects the disintegration time that can affect the availability of drugs in the body [18].

The results of the granulated mass analysis showed that all parameters of both formula A and B complied to the pharmaceutical requirements (Table 5). Except for the compressibility value of Formula B (22.9%). That was slightly higher than the requirement (21%). The compressibility value may be influenced by the use of explotab as a disintegrant material. Compressibility test aims to measure the density of powders granules to facilitate tablet compressing, because it is commonly tablets with a good percent compressibility value will be easier to compress [30]. Furthermore, the results of the physical analysis of the both tablet formula (Table 6) showed that the formula B containing an explotab material as disintegrant were better than that of formula A (amprotab). The result of physical analysis of tablet B provided better of the pharmaceutical requirements, such as, disintegration time (13–15 min), friability (0.7%) and mean weight (767 mg) that was close to the targeted tablet weight, 780 mg.

Amprotab or abbreviation of starch pro tablet is a tablet excipient in the market that is generally made from cassava/manihot. This material is widely used in the manufacture of tablets because some advantageous of this material, such as, more economical, easy to obtain, white in color and inert. Starch can function as a filler, crusher and binder. The function of this starch as a disintegrant is commonly through the mechanism of granule development due to contact with water. In addition, the capillary properties of starch and the repulsive force between particles in the tablet when in contact with water increase the disintegration of the tablet [18]. Explotab is a tablet excipient from the modified starch group that known as super-disintegrant. The presence of a carboxymethyl group enhances

hydrophilicity but does not cause it to dissolve completely in water. When contacted to water, the compound will extend while maintaining its integrity, accelerating tablet broken. Explotab is typically suited as a disintegrator material in dry granulated method [18, 31]. The physic-chemical process of explotab had the impact that this compound exhibited a disintegrant properties better than that of amplotab. However, it must be taken into account that explotab is more costly than amprotab.

5 Conclusion

The final tablet dosage form containing FE, a combination of secang and gambir extract, had been obtained. The use of explotab as a disintegrant material was able to provide a tablet that met pharmacopeia requirements. This pharmaceutical dosage form, proven to overcome hyperuricemia, had the potential to be produced on a larger scale. However, in-depth studies are required to understand more on the dissolution properties of the active compounds of the final dosage form.

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