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Original Research Article

Evaluation of Film-Coated Tablets of Ethyl Acetate Fraction of *Uncaria gambir* (Hunter) Roxb

Nanang Yunarto[1,2]*, Indah Sulistyowati[3], Berna Elya[1], Rani Sauriasari[1], Laurentia K. Mihardja[4,5]

[1]*Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia*
[2]*National Institute of Health and Research Development, Jakarta, Indonesia*
[3]*Center of Health Resilience and Resource Policy, Jakarta, Indonesia*
[4]*National Research and Innovation Agency of the Republic of Indonesia, Jakarta, Indonesia*
[5]*Faculty of Medicines, University of Malahayati, Lampung, Indonesia*

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ABSTRACT

Gambir (*Uncaria gambir* [Hunter] Roxb) is a plant that can effectively treat hyperlipidemia. Its pharmacological effect is influenced by the high concentration of catechin, the major active compound, especially in the ethyl acetate fraction of gambier (EAFG). The EAFG can be utilized commercially, and it is produced into film-coated tablets to boost its stability because catechins are less stable when exposed to humidity and light. The present study was conducted to produce EAFG film-coated tablets and evaluate their physicochemical characteristics and stability during storage. Gambir leaf extract was prepared and fractionated with ethyl acetate as a solvent. The EAFG was granulated, followed by the tablet compacting and coating processes. The film-coated tablets of EAFG were subjected to physicochemical evaluation, dissolution, and accelerated stability tests. The physicochemical analysis revealed that the film-coated tablets met the standards for general appearance, hardness, friability, disintegration time, and catechin content. After 60 minutes, the dissolution profile of EAFG revealed that at least 75% of the catechin was dissolved in the media at pH 1.2, 4.5, and 6.8. Accelerated stability studies indicated good stability over six months. The formulation demonstrated no changes in the physicochemical properties of EAFG film-coated tablets. The development of film-coated tablets of EAFG showed good quality in terms of physicochemical, dissolution, and stability during storage. This is suitable for improving catechin's moisture and light protection.

***Keywords*:** Catechin, Film-coated tablet, Dissolution profile, Stability, *Uncaria gambir*

Introduction

Hyperlipidemia is one of the main risk factors for cardiovascular disease. In 2020, approximately 19.1 million people died from cardiovascular disease, representing 32% of all global deaths. Coronary heart disease (CHD) caused 85% of these deaths, which included heart attacks and strokes. This shows that CHD is a serious problem that must be addressed.[1] Statins are the first-line treatment for hyperlipidemia. Simvastatin is the most commonly used statin medicine in the community; however, long-term use might cause negative effects. Long-term simvastatin use has been linked to side effects, such as headaches, muscle discomfort, and gastrointestinal issues.[2] As a result, more study is needed to identify natural raw materials that have the same effects as synthetic medications while having fewer negative effects.

One of the compounds that is effective as a hyperlipidemia drug is catechin. A native Indonesian plant that contains a lot of catechins is gambir (*Uncaria gambir* [Hunter] Roxb). Gambir leaves were fractionated using ethyl acetate, methanol, and water solvents, with ethyl acetate solvents having the greatest catechin content, which exceeded 90%.[3]

*Corresponding author. E mail: berna.elya@farmasi.ui.ac.id
Tel: +62-81314161497

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Catechins from gambir leaves have high antioxidant activity.[4] They can inhibit the activity of the HMG-CoA reductase and lipase enzymes. The inhibitory activity of catechins increases with their concentration, lowering total cholesterol levels.[5] The development of raw materials in the form of the ethyl acetate fraction of gambir leaf extract will improve the quality of raw materials due to the high catechin content in the ethyl acetate fraction of gambir (EAFG), cleaner physical appearance, lower water, and ash content. Catechin compounds are less stable in the presence of humidity and water, making them more easily oxidized.[6] Also, catechins are less stable to UV light and visible light.[7] One effort to increase the stability of catechins in EAFG is by formulating them in film-coated tablet dosage forms. Film-coated tablets can increase product stability by containing active substances sensitive to moisture and light and easily oxidized.[8]

The present study aimed to produce and evaluate film-coated tablets made from the ethyl acetate fraction of gambir leaves. The quality of film-coated tablets was assessed based on their physicochemical properties, drug release, and stability during storage.

Materials and Methods

Preparation of gambir leaf extract

The extract of gambir leaves was prepared from plants obtained from Mungka District, Payakumbuh, West Sumatera, Indonesia. The plant leaves were identified and authenticated by Dr. Nuraianas, Head of Herbarium Laboratory, Department of Biology, Andalas University, Padang, Indonesia, with ID No. 024/ANDA/II/2022.

Equipment and chemical materials used for the study

The equipment used includes a super mixer (Jaw Chuan), a fluidized bed dryer (Hong Dau), an oscillating granulator (Yenchen), a cone

mixer (Canaan), a tableting press machine (Jen Chiang), a tableting coating machine (Hong Dau), an ultra-mixer (Turrax), a high-performance liquid chromatography (HPLC; Waters), a dissolution tester (Hanson), a hardness tester (Erweka), a friabilator (Erweka), an analytical balance (Metler Toledo), a disintegration tester (Erweka), and a climatic chamber (Memmert). The materials used included avicel PH 102 (DuPont Pharma), polyvinyl pyrrolidone 30 (BASF), primellose (DFE Pharma), kollidon CL (BASF), magnesium stearate (BASF), cab–O–Sil (BASF), Opadry aqueous moisture barrier (AMB II; Colorcon), catechin standard (Sigma), dissolution medium (pH 1.2, 4.5, and 6.8; Sigma), trifluoroacetic acid (Merck), methanol (Merck), acetonitrile (Merck), and aquabidest.

Fractionation of gambir leaf extract
Fractionation of gambir leaf extract was carried out by macerating gambir leaf powder in a chromatographic column using ethyl acetate as the solvent. The faucet on the column was slightly opened, and the EAFG leaf extract was collected using an Erlenmeyer flask. The resultant fraction was concentrated with a rotary evaporator and dried in an oven at 40-50ºC for 20-30 min.[9]

Granulation
All raw materials were weighed, and then the gambir leaf ethyl acetate fraction and avicel PH 102 were put into the super mixer and stirred at low speed for 2 minutes. Then, primellose (inner phase) and kollidone CL were added to the super mixer and stirred until homogeneous at low speed for 2 minutes. After that, polyvinyl pyrrolidone 30 was added, which had earlier been dissolved in 6 L of 96% ethanol, through the mixer funnel and gradually flowed into the super mixer while stirring for 2 minutes at low speed. The mixing was continued at high speed for 5 minutes. The granules were removed from the super mixer. The granulate was dried in a fluidized bed dryer (FBD) at 50°C for 3 minutes. In the next stage of granulation, the granules were added to a mixture of primellose (outer phase), cab oil, and magnesium stearate and mixed until homogeneous using a cone mixer for 5 minutes. Before the molding process was carried out, the granules were tested for water content, flow rate, angle of repose, compressibility index, and Hausner ratio.

Tablet compacting and coating process
The EAFG granules were compacted using a round biconvex punch with a diameter of 13 mm and a tablet weight of 700 mg. The tablet coating suspension was composed of a polymer in the form of Opadry AMB II, which was used to coat 70 kg of tablets. A total of 2.1 kg of AMB II Opadry was gradually added into a stainless-steel bucket containing 10.5 L of water while stirring using an ultra-mixer at low speed for 15 minutes. The coating process began by heating the coating pan to an inlet temperature of 50-60°C for 3 minutes. Then the core tablet was inserted, and the coating pan was rotated at a speed of 10 rpm for 5 minutes. Coating with Opadry AMB II coating suspension was carried out with the following parameters: pan speed of 14 rpm, compressor pressure of 50-70 psi, inlet temperature of 60-65°C, tablet temperature of 45-48°C, spray gun distance to the tablet of 20-25 cm, spraying speed of 40-60 g/minute. After spraying the coating liquid, the tablet was dried in the coating pan for 5 minutes. The film-coated tablets were evaluated for physical appearance, diameter, weight, hardness, friability, disintegration time, and active component content.

Catechin assay test
Twenty tablets were weighed, the average weight was obtained, and the tablets were crushed until smooth. The crushed material was weighed at 7 mg and placed in a 50-mL measuring flask. Then, 30 mL of methanol solvent was added and sonicated until dissolved. Following sonication, methanol was added and homogenized. The test solution was filtered through a 0.45 µm filter and placed in an HPLC vial. A reference solution was prepared by weighing 5.0 mg of standard catechin, and placing it in a 50 mL volumetric flask. Then, 30 mL of methanol solvent was added and the sonication continued until the compound completely dissolved. The sonicated solution was then added to the methanol solvent, which was then homogenized. The homogenized solution was filtered through a 0.45 µm filter and placed in an HPLC vial. The concentration was determined by HPLC using a Sun Fire C18 4.6 x 150 mm column, at a flow rate of 0.45 mL/minute, an injection volume of 1.0 µL, and UV detection at 280 nm. The mobile phase was used in a gradient with mobile phases A: 0.1% trifluoroacetic acid in a mixture of acetonitrile and water (5:95) and B: 0.1% trifluoroacetic acid in acetonitrile. Gradient conditions included 0-4 minutes (100% A), 4-20 minutes (71.5 A: 28.5 B), and 20-30 minutes (100% B).[9]

Dissolution of a coated tablet test
The dissolution test was performed in the acid medium at pH 1.2, buffer pH 4.5, and buffer pH 6.8. The volume of each medium was 900 mL, and the dissolving tester was a Hanson Vision G2 Elite type II (paddle). The dissolution medium was maintained at a temperature of 37 ± 0.5°C and a paddle stirrer speed of 75 rpm. Aliquots of 10 mL were taken at intervals of 15, 30, 45, and 60 minutes. The aliquots were tested for catechin levels using HPLC. For film-coated tablets made from herbal preparations, the active substance content is required to be no less than 75%.[10]

Stability testing
The stability test of EAFG film-coated tablets in this study was carried out using an accelerated stability test. Indonesia includes climatic zone IVb, which has hot temperatures and considerable humidity. Accelerated storage stability tests were performed in a climatic chamber at a temperature of 40°±2°C and a relative humidity (RH) of 75±5% with test times of 0, 3, and 6 months. The test parameters carried out included general appearance, hardness, friability, disintegration time, and catechin content.[11,12]

Statistical analysis
One-way ANOVA and student t-test statistical analysis were performed using GraphPad Prism 5, version 5.01 to compare the difference in data and a p-value < 0.05 was considered significant. Tukey's Post Hoc test was used to compare means of pairs to identify where the exact difference lies from the result obtained from the One-way ANOVA analysis.

Results and Discussion

The process of fractionation was carried out with 10 kg of gambir leaves, yielding 7.44 kg of dried ethyl acetate fraction powder with a yellowish color. From the fractionation data, the yield was calculated to be 74.4%. The yield percentage result meets the standards in the Indonesian Herbal Pharmacopoeia.[13] The results of this study were much higher than those of Kurniatri *et al*. The yield was only 63%.[14] Fractionation and evaporation processes were optimized by using equipment from GMP facilities. Water content, flow rate, angle of repose, compressibility index, and Hausner ratio were all determined during the granule evaluation. The granule mass evaluation results are shown in Table 1. In testing the granule water content, the result obtained was 3.78 ± 0.07%. The water content of the granules must be maintained so that they are not too dry because this can cause capping or lamination due to a lack of cohesion between the particles. Maintaining sufficient humid conditions promotes good bonding between particles and helps to prevent capping or lamination.[15] Flow rate testing was obtained at a granule flow rate of 11.77 ± 0.35 g/sec, while measurements of the angle of repose of the granules were obtained at 28.80 ± 0.80°. Flow time affected the tablet printing process. If the granule has good flow properties, it will produce uniform tablets. A good flow time indicates the speed at which the granules consistently fill the compression space, minimizing holes or pores in the tablet and resulting in a uniform weight.[16] Based on the angle of repose, granules were in the very good category since they were in the 25-30 range.

Table 1: Evaluation of granules

Properties	Result
Loss on drying (%)	3.78 ± 0.07
Flow rate (g/sec)	11.77 ± 0.35
The angle of repose (°)	28.80 ± 0.80
Compressibility index	13.91 ± 0.03
Hausner ratio	1.16 ± 0.01

The angle of repose correlates with interparticle friction and flowability of cohesive materials and is used to characterize bulk powders. The smaller the angle of repose, the better the flow characteristics of the granules, resulting in a uniform tablet weight.[17] Based on testing, the granule compressibility index value is 13.91 ± 0.03%, and the Hausner ratio is 1.16 ± 0.01. The granule is in a good category because it has a compressibility index value between 11 and 15 and a Hausner ratio between 1 and 1.12. The compressibility index is a fast indirect method for measuring the relative forces between particles and the friction force of bulk powders. In general, the lower the compressibility index value, the better the powder flows.[18] Hausner ratio testing indicates the ability of the bulk powder to rearrange the spaces between particles that appear during external forces such as knocking or vibration. The rearrangement of powder particles into the interparticle spaces depends on the cohesive strength of the powder, which can be expressed as the Hausner ratio.[19] By evaluating these results, it can be inferred that the granules have good flow properties, as they flow freely and can be molded into tablets of uniform weight. The evaluation of the physical and chemical properties of the coated tablets was carried out, and the results are presented in Table 2. The physical quality tests included tablet weight, disintegration time, hardness, and friability. Tablet weight testing is intended to ensure that tablets are made with accurate size and uniformity in the content of the formulation. Tablet weight is a very important parameter in tablet quality because it affects the uniformity of active substance levels. The weight test results of EAFG film-coated tablets were within the weight range specifications. The US Pharmacopeia has established weight standards for traditional medicine tablets that must be met, including that there must be no more than two tablets, each of which has a weight that deviates from the average weight by more than 5%, and not a single tablet whose weight deviates from 10% of the average weight. The increase in weight obtained after the coating process was 2.66%. This demonstrates that the coating technique is extremely effective, as the weight increase of the film-coated tablets falls within the specified range of 2-3%. According to Teckoe *et al*. (2013), coating with Opadry AMB with a weight increase of more than 2% results in a uniform tablet color and effectively protects the core tablet from moisture.[20] Furthermore, using Opadry AMB as a coating material provides advantages, such as consistent color formulation and the ability to provide a good tablet coating layer, resulting in an excellent tablet appearance.[21]

The EAFG film-coated tablets were also evaluated for hardness and friability. The hardness of film-coated tablets increased slightly during the coating process. This is because the coating mass-produced adhesion bonds on the tablet surface, which contributed to increasing the hardness of the tablet and the force required to break the coating layer. The friability test measures weight loss caused by abrasion on the tablet surface.[22] The test results demonstrated that EAFG film-coated tablets exhibited excellent friability, at 0.02%. This result is consistent with the findings of Yunarto *et al*. (2016), who observed that Opadry AMB II coating material in the formulation of dihydroartemisinin-piperaquine (DHP) film-coated tablets was able to keep the tablets strong and not brittle with a friability value of 0.02%. A good tablet has a friability of no more than 1%.[23] The disintegration time of film-coated tablets needs to be determined to ensure that the tablet disintegrates swiftly enough to facilitate its dissolution in the gastrointestinal tract. When the tablet is dissolved, it can then be absorbed into systemic circulation. Based on the disintegration time test, EAFG film-coated tablets disintegrated quickly, taking 5.48 ± 0.20 minutes. The disintegration time for traditional medicine film-coated tablets should not exceed 60 minutes. The disintegration times for the core and coated tablets were not significantly different. However, the core tablet was slightly lower. This was achievable because the surface pores of the core tablet were covered with coating material so the disintegration test media would take longer to penetrate the tablet. The use of a film coating does not have much effect on the disintegration time of the tablet because the layer formed is quite thin. The disintegration time will only be affected if the coating material used is large enough and the layer formed is thick in the coating process.

Table 2: Physicochemical properties of the core and film-coated ethyl acetate fraction of gambir tablets

Properties	Requirement	Core tablets	Film coating tablets
Average weight (mg)	Core: 665-735 Coated: 685-757	699.15 ± 3.53	717.76 ± 3.33
Weight gain (%)	3	-	2.66%
Diameter (mm)	13.00-13.20	13.08 ± 0.004	13.12 ± 0.004
Thickness (mm)	5.00-5.50	5.24 ± 0.012	5.30 ± 0.014
Hardness (kp)	> 4	16.93 ± 2.24	17.03 ± 2.43
Friability (%)	< 0.3	0.02	0.02
Disintegration time (min)	< 30	5.24 ± 0.30	5.48 ± 0.20
Catechin content (%)	90-95	94.20 ± 0.24	94.22 ± 0.50

Table 3: Accelerated stability testing of ethyl acetate fraction of gambir film-coated tablets

Properties	Month 0	Month 3	Month 6
Appearance	Round, biconvex, brown	Round, biconvex, brown	Round, biconvex, brown
Diameter (mm)	13.12 ± 0.004	13.12 ± 0.005	13.12 ± 0.005
Thickness (mm)	5.30 ± 0.014	5.30 ± 0.013	5.30 ± 0.011
Weight (mg)	717.76 ± 3.33	718.02 ± 3.47	717.51 ± 3.32
Hardness (kp)	17.03 ± 2.43	17.24 ± 2.68	17.18 ± 2.32
Friability (%)	0.02	0.03	0.03
Disintegration time (minutes)	5.48 ± 0.20	5.12 ± 0.45	5.26 ± 0.33
Catechin content (%)	94.22 ± 0.50	94.05 ± 0.22	94.12 ± 0.14

Large amounts of water vapor can be retained in the coating layer by increasing its thickness.[24] The active substance content in film-coated tablets was 94.22 ± 0.50%. Catechin levels in core and film-coated tablets are relatively similar. This demonstrated that the use of Opadry AMB tablet coating material does not affect the catechin content of film-coated tablets. These results are consistent with those of Min *et al*. (2019), who discovered that coating with Opadry AMB did not influence choline alfoscerate levels in film-coated tablet formulations.[25] The results of the accelerated stability tests shown in Table 3, the film-coated tablets met all test parameters. The use of coating materials in this formula can maintain the physical and chemical stability of the finished goods. Stability tests on traditional medicines are carried out to determine the shelf life of finished products and their packaging systems under specified storage conditions. While packaging design including the use of desiccants is part of the strategy to maintain the stability of drugs that are susceptible to hydrolysis, special moisture protection films such as Opadry AMB II can provide additional protection against moisture. This is suitable for protecting products whose active substances are hygroscopic in areas with high humidity.[26]

Dissolution testing on EAFG film-coated tablets was carried out by estimating the levels of catechins that dissolved in the dissolution medium. The tests were performed in three different media that replicated bodily fluids at the location of drug absorption. The acid medium at pH 1.2 represents the gastric fluid, the buffer medium at pH 4.5 represents the duodenal fluid, and the media at pH 6.8 represents the jejunum and ileum fluid.[27] The results of the EAFG film-coated tablet dissolution test are shown in Figure 1. Based on the results of the dissolution test in the three media for all tablet samples at the 15th minute, considerable amounts of catechin were dissolved, and by the 60th minute, all had dissolution levels greater than 75%. The Indonesian Food and Drug Agency does not specify dissolution levels as a testing parameter for film-coated tablets for traditional medicines, while the United States Pharmacopeia mandates that active ingredients in traditional medicines dissolve at least 75% within 60 minutes.[10] The good dissolution rate in the present study is consistent with the physical test of the dissolution time of film-coated tablets, which was 5.48 minutes. The disintegration time could affect the dissolution rate of a drug. The drug will dissolve faster if it also degrades quickly. Therefore, the higher the disintegration rate of a tablet, the faster the drug dissolves. The dissolution test was performed to support the dissolution time test data because the dissolution time only indicates how long it takes for the tablet to disintegrate into small particles and does not guarantee that these small particles will release the drug substance in solution at the proper rate.[28] A dissolution test is essential for a formulation because it produces a dissolution rate that is proportional to the efficacy of the drug. According to the results of the accelerated stability test, the film-coated tablet met all test conditions. The use of coating materials in this formula can maintain the physical, chemical, and microbiological stability of the preparation. Stability tests on traditional medicines are carried out to determine the shelf life of finished products and their packaging systems under specified storage conditions. While desiccants are used in packaging to ensure the stability of hydrolysis-prone pharmaceuticals, specific moisture protection films, such as Opadry AMB II can provide extra moisture protection. This is appropriate for protecting hygroscopic materials and high-humidity locations.[29] Opadry AMB II is a coating made from a polyvinyl alcohol polymer. This coating ingredient acts as a moisture barrier, preventing the absorption of water or water vapor into the tablet. The polyvinyl alcohol polymer molecule absorbs water and binds it with hydrogen bonds, preventing it from penetrating the core tablet.[30] Catechin dissolves well in the acid medium at pH 1.2 and buffer 4.5, although it dissolves slower in buffer medium at pH 6.8. This demonstrates that the pH of the dissolution medium affects the catechin's dissolution rate. These results are in agreement with the findings of Chen *et al*.,[31] who observed the chemical stability of catechins in water solvents and alkaline pH, including pH 8.81 to 10.52. This study showed that catechin dissolved in an air-free basic solvent experienced a change in spectrum. This change in spectrum occurs because the catechin oxidation reaction forms quinone metabolites, and the catechin oxidation reaction increases with increasing pH. The oxidation process of a chemical can be influenced by its pH sensitivity. Catechins are weak acids; acidic compounds are unstable at neutral to alkaline pH conditions because deprotonation occurs in the hydroxyl groups of catechins.[30]

Conclusion

The findings of this study revealed that the development of film-coated tablets of the ethyl acetate fraction of *Uncaria gambir* is suitable for increasing the moisture and light protection of catechin. Moreover, film-coated tablets have good physicochemical properties, solubility, and stability during storage. The present study could support the development of a pharmaceutical moisture barrier film coating system for catechin-containing immediate-release tablets.

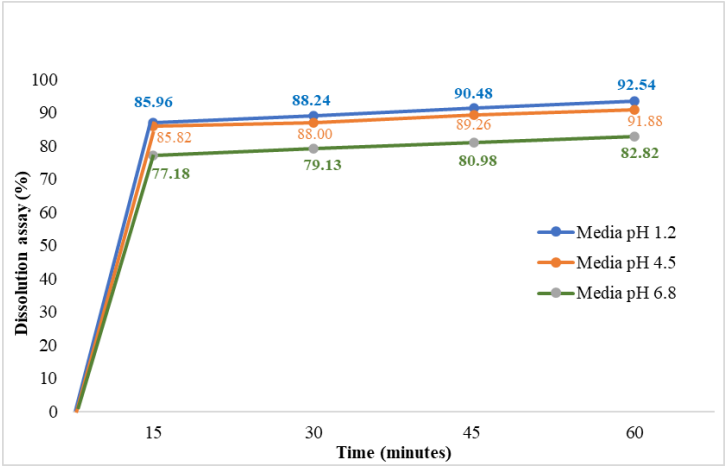

Figure 1: Dissolution profile of ethyl acetate fraction of gambir film-coated tablet in pH 1.2, 4.5, and 6.8 media.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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