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Evaluation of Dosage Properties and Irritation Test of Ambon Banana Peel Methanol Extract Gel with Various Concentrations of HPMC as Gelling Agent

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Abstract
Banana is one of Indonesia's plant products that have great potential but has so far received little attention. Ambon banana peel waste and other banana peel waste are generally thrown away. Preparations in the form of gels are more popular because they cause an incredible feeling on the skin, are easy to dry, and are easy to wash. In gel formulas, a critical factor affecting the physical properties of the gel is the use of a gelling agent. HPMC can provide good viscosity stability at room temperature even though it is stored for a long period. Gel formulations were made with varying concentrations of HPMC 0.5%, 1%, and 3%, and then evaluated the properties of the preparation which included an organoleptic test, homogeneity test, viscosity test, pH test, and spreadability test as well as irritation test on male Wistar rats. The results showed that the variation of HPMC concentration in the preparation of ambon banana peel methanol extract gel could affect the physical properties of the practice. The higher the concentration of HPMC, the thicker the gel texture and the higher the viscosity value. The variation of HPMC concentration in the preparation of methanol extract gel of ambon banana peel does not affect the effect of irritation on the skin which can be shown in the results of *in vivo* irritation testing on male Wistar rats. The test results show the absence of erythema and edema.

Keywords: Ambon Banana Peel, Gel, HPMC, Gelling Agent

Introduction

Mittermeier (2005), Indonesia has the second largest biodiversity in the world. Banana is one of Indonesia's products that has great potential but has so far received little attention. Banana trees are easy to plant, can grow in both high and lowlands, do not require much fertilizer and reproduce by sprouting and growing around the parent tree, so banana trees are almost in every garden [1]. Ambon banana peel waste and other banana peel waste are generally thrown away. Processing ambon banana peel by extraction for gel making is an interesting thing in addition to waste utilization can also be used for treatment. The active substances in ambon banana peel that play a role in the wound healing process are flavonoids, tannis, saponins, and alkaloids [2]. Several previous studies have shown that flavonoids are believed to be one of the important components in the wound healing process. Tannins have the ability as antimicrobials and can increase epithelialization. Steroids are anti-inflammatory [3]. Saponins can accelerate the wound healing process due to antimicrobial activity and antioxidant properties [4].

According to research by Yulis *et al*. (2020), methanol solvent is most effective in extracting compounds found in ambon banana peel. Extracts form methanol solvents can quickly show more significant color changes in the identification process of four types of secondary metanolites namely flavonoids, phenolics, tannins, and saponins [5].

Gel is a pharmaceutical preparations in the form of a semisolid consisting of particles of a dispersion composed either of small inorganic particles or large organic molecules and mutually impregnates with liquid [6]. Gel preparations are more popular because they cause a cool feeling on the skin, are easy to dry and easy to wash [7]. Other advantages of gel preparations include being easy to spread when applied to the skin, giving a cold sensation, and not causing marks on the skin [8].

Based on this, research was conducted related to the formulation of gel preparations of methanol extract of ambon banana peel. The difference in concentration of HPMC gelling agent in this study is to determine whether there is a difference in the properties of the gel preparation of methanol extract of ambon banana peel (*Musa paradisiaca*) and to determine the optimum concentration of HPMC so as not to cause irritation to the skin. There have been many studies related to ambon banana peel extract gel but each study has its own characteristics related to the theme. Both form the type of preparation, the ingredients used, and the method of manufacture. The focus of the research studied is related to the concentration of HPMC gelling agent used, not many studies have been conducted related to the use of HPMC in the preparation of banan peel methanol extract gel.

Materials and Methods

Materials

Ambon banana peel (*Musa paradisiaca*), methanol, aquadest, HPMC, glycerin, phenoxyethanol, TEA, HCl, mayer reagent, ethanol, $FeCl_3$ 5%, male wistar rats aged 2-3 months with body weight of 100-200 g,

Methods

1. Ethical Clerance

Taking care of the ethical feasibility of using test animals for research purposes at the Ethics Commission Dr. Moewardi Hospital Surakarta.

2. Sample Preparation

Ambon bananas were obtained form banana selling centers in the Surakarta area as much as 2 kg. sampling was done by separating the banana peel form fruit and taking the inside of the banana peel.

3. Determination

Determination of ambon banana peel samples by matching the morphological characteristics of the samples with the literature conducted at the Laboratory of Faculty of Mathematics and Natural Sciences, Sebelas Maret University. Determination aims to determine the truth of the plant and avoid errors in collecting materials and the possibility of mixing materials with other plants.

4. Extraction of Ambon Banana Peel

Wet ambon banana peel as much as 200 gram was pulverized with a blender so that it became porridge. The banana peel pulp was put into a container and extracted bt maceration. Maceration was carried out with methanol solvent with a ratio of banana peel: methanol (1:5) for 3 days and evey day stirring obtained was then filtered and thickened with a rotary evaporator and waterbath [9].

5. Gel Preparation of Methanol Extract of Ambon Banana Peel

The gel base was prepared with variations of HPMC concentrations of 0, 5%, 1%, and 3% Table 1.

Table 1: Gel preparation formula of methanol extract of ambon banana peel

Material	Concentratuon of Ingredients in Gel Base Formulation				Description
	F1	F2	F3	F4	
HPMC	0, 5	0, 5	1	3	*Gelling agent*
Glycerin	10	10	10	10	Humectan
Phenoxyethanol	0, 5	0, 5	0, 5	0, 5	Preservatives
TEA	0, 5	0, 5	0, 5	0, 5	Excipient
Ambon banana peel extract	-	1	1	1	Active substance
Aquadest	Ad 100	Ad 100	Ad 100	Ad 100	Solvent

HPMC was developed with heated aquadest. TEA was mixed with the expanded HPMC (Mass I). phenoxyethanol was dissolved with heated aquadest. Add glycerin (Mass II). Mix mass I and mass II, ad aquadest little by little to form a gel base, then methanol extract of ambon banana skin plus the remaining hot aquadest and added to the finished gel base and then crushed until homogeneous.

Organoleptical and Homogeneity Observations

Organoleptical observations were made visually including odor, color, and texture. Homogeneity observations were made by placing a number of samples on an object glass.

Viscosity Observations

Viscosity measurements were made using a Brookfield viscometer. Viscosity measurements were made by placing the sample into the Brookfield viscometer and the setting spindle number 4 and speed 6 rpm. The viscosity of the gel will be read when the Brookfield viscometer is run [10].

PH Test

The pH test of the gel was conducted using a pH meter. The device was first calibrated with standard aqueous solutions of pH 4 and pH 7 being used for the gel pH test [11].

Spreadability Test

A total of 0.5 gram of preparation was placed in the center of a round glass scale, then covered with another round glass. Measurement of the diameter of the spread of the preparation longitudinally and transversely, and carried out every free addition of 50-150 gram. The qualified spreadability is 5-7 cm [12].

6. Irritation Test

Before being treated, the test animals that will be used, namely wistar rats, are given the opportunity to adapt to their new environment (acclimatization). The acclimatized rats were each shaved on the back with an area of 3x3 cm. Furthermore, right in the middle of the shaved back, a box mark was made as an application area with an area of 2x2 cm for each test area [13].

The test animals were given the finished sample of the methanol extract gel of ambon banana peel on the back area. The sample was administered for 24 hours by wrapping it with gauze and bandage and the covered with occlusive patch. After that, observations were made for the preliminary for 24 hours, then continued to the main test. Observations in the main test on rat skin began on days 1 and 3. Furthermore, observation continued on day 5 to see the reaction of erythema and edema [14].

Table 2: Erythema and Edema Parameters

Erythema		Edema	
Type	Value	Type	Value
No erythema	0	No edema	0
Slight eritema	1	Very mild edema	1
Erythema is evident	2	Mild edema	2
Moderate to strong erythema	3	Moderate edema (± 1 mm thickness)	3
Severe erythema (sores)	4	Severe edema (>1 mm)	4

The data obtained were then analyzed to obtain the Primary Irritation Index (PII) using the formula:

$$PII = \frac{\text{Sum of all erythema and edema values}}{\text{Number of rat} \times \text{number of observation time}}$$

PII values are used to determine the level of irritation in the following table:

Table 3: Primary Irritation Index (PII)

Category	Primary Irritation Index
Meaningless	0 - 0,4
Low irritation	0,5 – 1,9
Moderate irritation	2 – 4,9
Severe irritation	5,0 – 8,0

Results and Discussion

1. Extraction of Ambon Banana Peel

Extraction is a process of filtering an active compound from a vegetable or animal material or simplisia using a certain suitable solvent. This extraction can be done by various methods, according to the nature and purpose [15]. The solvent used in this study is methanol because methanol can dissolve polar and nonpolar compounds so that it can extract secondary metabolite compound contained in the samples used [16]. The use of a solution as a solvent in the extraction process of a material, gives better results of aquadest extraction [17]. Alkaloids, steroids, saponins, and flavonoids from plants can be drawn by methanol [18].

Ambon banana peels that have been mashed and macerated using methanol solvent with a banana peel: methanol ratio (1 5) for 3 days and every day stirring, the filtrate is then filtered and thickened so that the extract is obtained. The extract obtained was then concentrated into a thick by evaporating the solvent until the extract became thick using a rotary evaporator and waterbath. The rotary evaporator process is carried out at a temperature below the boiling point of methanol, which is 64.7ºC. The temperature used is 50-60ºC because it increases the solvent evaporation process and is expected not to damage the antioxidant compounds in the extract [19]. The purpose of concentrating the extract using a rotary evaporator and waterbath to remove the solvent.

The thickened extract was observed organoleptically to determine the physical properties of the thickened extract of ambon banana skin in the texture, color, and odor which can be seen in Table 4.

Table 4: Observations of Organoleptic Ambon Banana Peel Thickened Extract

Organoleptic	Results
Texture	Thick
Color	Brown-black
Odor	Typical banana

2. Gel preparation of Methanol Extract of Ambon Banana Peels

Methanol extract of ambon banana peel was formulated in gel preparation, using HPMC gelling agent, with concentrations of 0.5%, 1%, and 3%. In gel preparation, an important factor that affects the physical properties of the gel is the gelling agent. HPMC is a hydrophilic gel base that can be absorbed or dissolved in water. In addition to HPMC as a gelling agent, several ingredients are used, such as glycerin as an emollient and humectant in topical preparations with a concentrasion range of 0.2-65.7% [20]. The addition of TEA which is used as a neutralizing and clarifying agent that is alkaline, increases pH and viscosity. HPMC is a semi-synthetic cellulose-derived gelling agent that is resistant to phenol, stable at pH 3-11 can form a clear gel that is neutral and has a stable viscosity in long-term storage [21]. Topical preparations also need to be added with preservatives, the preservative used is phenoxyethanol. Phenoxyethanol is a preservative that is often used in drugs, cosmetics, and other pharmaceutical products [22].

3. Sample Evaluation

Evaluation of the physical properties of the methanol extract gel preparation of Ambon banana peel carried out is organoleptic test, homogeneity test, viscosity test, pH test, and spreadability test. Organoleptic test of the gel preparation of methanol extract of Ambon banana peel observed are texture, color, and odor. The resulting preparation should have a good texture, attractive color, and pleasant smell. The results obtained on organoleptic testing of ambon banana peel extract gel preparations can be seen in Table 5.

Table 5: Observations of organoleptic gel preparations

Observations	F1	F2	F3	F4
Texture	+	+	++	+++
Color	Clear	Clear slightly brown	Clear slightly brown	Clear slightly brown
Odor	No odor	No odor	No odor	No odor

Description: (+) liquid (++) Slightly (+++) Viscous

Organoleptic test is one of the quality controls for semisolid preparations, especially ambon banana peel methanol extract gel by observing the texture, color, and odor of the preparation which can be seen in Table 5, organoleptic examination of texture shows that the four formulations have different textures in F1 and F2 have a liquid texture, F3 has a slightly thick texture, and F4 has a thick texture. The difference in texture is due to the different concentration of gelling agent used. A low concentration of HPMC will cause the gel preparation to be liquid, and vice versa, a high concentration of HPMC will cause the gel preparation to be thick. Organoleptic examination of color, in F1 is clear and F2, F3, and F4 are slightly brownish clear. The difference in color in this preparations is because F1 does not add extract and the other three formulations do add extract.

Gels that meet organoleptic requirements have a color like the active substance, odorless, and thick texture. The results of organoleptic testing showed that each formulation had varying viscosity. This has several factors that can influence, namely the process of mixing ingredients and differences in HPMC concentration in each formulation. In addition, the more the addition of liquid substances, the preparation will also be liquid. The greater the concentration of gelling agent or gelling agent added in a preparation, the thicker the preparation will be.

The homogeneity test is carried out to see the mixing of the ingredients contained in the gel preparation (homogeneous) so that at the time of use it can seep and enter the skin without feeling the presence of fine grains that interface with use, from the observation of the four formulas, it shows that all gel preparations are homogenous, characterized by the absence of particles or fine grains on the glass object [11]. The homogeneity test has a requirement that there are no coarse grains in the gel preparation on the glass object. The aim is to ensure that the gel preparation has the same uniformity. The results of the gel homogeneity test show the absence of lumps or particles in the preparation, so it can be said that all formulas produce homogeneous gels. The stirring speed aims to reduce the particle size so that each particle has the same opportunity to be in every part of the

gel. The results of the F1 to F4 homogeneity test found that the four formulas has a very good level of homogeneity, because the four formulas did not have coarse grains on the glass object.

The viscosity test aims to measure the viscosity value or viscosity of the gel preparation made and to determine whether or not the gel is smeared on the skin, the lower the viscosity, the easier the gel is applied to the skin while the higher the viscosity value, the hidher the viscosity level of the substance [23]. This viscosity test was conducted using a brookfield viscometer with spindle number 4 and speed 6 rpm. The results of the viscosity test observations can be seen in Table 6.

Table 6: Observations of viscosity gel preparations

Formulation	Viscosity (mPas)			Avarage
	Reps			
	1	2	3	
F1	245	247	246	246±1,0
F2	122	121	124	122,33±1,528
F3	1296	1300	1298	1298±2,00
F4	1211	1210	1215	1212±2,646

According to Rahmatullah *et al* (2020), good gel viscosity has a range of 500-10.000 mPas. The more HPMC or gelling agent, the thicker it will be and the higher it will rise for the experiment, it was found that the average results of the viscosity test that formulas F3 and F4 met the requirements [24]. The results of the F3 viscosity test are higher that F4, this can occur due to several factors that can affect viscosity, namely temperzture, solution concentration, solute molecur weight, and pressure. Temperature is inversely proportional to viscosity, if the temperature rises then the viscosity will drop, and vice versa. The concentration of the solution is direcly proportional to the viscosity, a solution with a high concentration will have a high viscosity as well, because the concentration of many dissolved particles is higher and the viscosity is higher. Viscosity is direcly proportional to the molecular weight of the solute because the presence of a heaby solute will inhibit or give a heavy load on the liquid so as to increase viscosity and the higher the pressure, the greater the viscosity of a liquid [25]. Another factor that can affect viscosity values is human error so that the results obtained have relatively different errors from the literature.

The pH test is carried out to see how the pH the gel preparation that has been made is in accordance with the pH of the skin, neither too acidic nor too basic to avoid damage or problems caused to the skin. According to SNI 16-4399-1996, the pH requirements for topical preparations are 4, 5-8. Testing the pH of gel preparations is very important because there will be direct skin contact. The pH value obtained form all formulas has a pH value of 7 so it is still safe for the skin because is does not irritate or make the skin scaly. The results of Ph testing can be seen in Table 7.

Table 7: Observations of pH gel preparations

Formulation	pH			Average
	Reps			
	1	2	3	
F1	7,2	7,4	7,3	7,3±0,1
F2	7,3	7,2	7,5	7,333±0,1528
F3	7,2	7,3	7,1	7,2±0,1
F4	7,1	7,3	7,2	7,2±0,1

Table 7 shows that the four formulations have the same pH value. This shows that te addition of gelling agent does not significantly affect the chage in pH. The pH results of each concentrations so that when udes it cause a comfortable affect on the skin.

The spreadability test was conducted to determine the spread of the gel on the skin surface. The spreadability of the gel can determine its adsorption at the place of use, the better the spreadability, the more gel is adsorbed. The results of spreadability testing can be seen in Table 8.

Table 8: Observations of spreadability gel preparation

Formulation	Spreadability			
	Load			
	0	50	100	150
F1	4,25 cm	4,5 cm	5,3 cm	6,5 cm
	4,5 cm	4,8 cm	5,5 cm	6,7 cm
	4,45 cm	4,7 cm	5,35 cm	6,6 cm
Average	4,4±0,132	4,6±0,153	5,38±0,104	6,6±0,1
F2	4,5 cm	4,7 cm	5,5 cm	6,2 cm
	4,6 cm	4,75 cm	5,4 cm	6,3 cm
	4,7 cm	4,85cm	5,45 cm	6,5 cm
Average	4,6±0,1	4,76±0,07	5,4±0,05	6,3±0,15
F3	4,2 cm	4,5 cm	5 cm	5,3 cm
	4,3 cm	4,7 cm	5,2 cm	5,5 cm
	4,1 cm	4,5 cm	5 cm	5,3 cm
Average	4,2±0,1	4,56±0,12	5,06±0,12	5,36±0,12
F4	4 cm	4,3 cm	4,8 cm	5 cm
	4 cm	4,4 cm	5 cm	5,3 cm
	4,2 cm	4,5 cm	4,8 cm	5 cm
Average	4,06±0,12	4,4±0,1	4,86±0,12	5,1±0,17

The requirement in the spreadability test is that the spreadability must be in the range between 3-5 cm. the results of the spreadability test showed that the average spreadability for formula F4 had the smallest spreadability followed by F3, F2, and F1. The spreadability of the gel is also influenced by viscosity, the viscosity of the gel is inversely proportional to the resulting spreadability [26]. The thicker the preparation, the smaller the spreadability and vice verca if the preparation is liquid, the spreadability will be large. This occurs due to an increase in gel concentration which can increase the resistance of the gel to flow and spread [27]. Therefore, the higher the HPMC content or gelling agent concentration, the decrease in the quality of spreadability [28]. Formulas F1-F4 meet the requirements for good spreadability quality. Changes in the spreadability of gel preparations can be caused by various factors. Various factors that can affect changes in spreadability include the concentration of substances added. Temperature, stirring method, pH, particle size, and viscosity. The addition of different levels of extracts can change the consistency of the gel preparation.

4. Irritation Test

The irritation test is divided into 5 groups with different treatments for each group. In group I rats, the normal control is not treated only shaved. In group II rats, the negative control is rats smeared with gel containing only gel base (Formulation I). In group III rats, treatment I is rats smeared with gel containing 0.5% HPMC (Formulation II). In group IV rats, treatment 2 is rats smeared with gel containing 1% HPMC (Formulation III). In group V rats, treatment 3 is rats smeared with a gel containing 3% HPMC (Formulation 4).

This calculation results in a Primary Irritation Index (PII) analysis of 0, which means that the four gel formulations do not show any irritating effects in the form of erythema and udema on the skin so that they are safe to use in their use on the skin. The test results of PII values can be seen in Table 9.

Table 9: Observations of irritations gel preparations

Groups	Day 1		Day 2		Day 3 ke-3	
	Erythema	Udema	Erythema	Udema	Erythema	Udema
I	0	0	0	0	0	0
II	0	0	0	0	0	0
III	0	0	0	0	0	0
IV	0	0	0	0	0	0
V	0	0	0	0	0	0
Total	0	0	0	0	0	0
PII	0	0	0	0	0	0
Summary	Meaningless					

The *in vivo* irritation test was carried out using male wistar white rat test animals whose backs had been shaced and had met ethical requirments so that they were suitable for testing. Wistar male rats were used as research subjects because thet are a group of mammls so that are not much different from humans, have a fast response, are used male because they do not experience the estrus cycle so that the sample becomes homogeneous and is expected to be accurate [29].

Observation of irritation is based on the presence of erythema and udema on the skin of the rat's back. After calculating the erythema and udema scores, the primary irritation index category was calculated. Table 9 shows that in all experimental groups there is no irritation characterized by the absence of erythema and udema. On the skin of the rat's back the socre or primary irritation index is zero (0), so it is included in the meaningless category. This shows that the dour formulations do not cause irritating effects on the skin so it is safe to use. In addition, the ingredients used have a synergistic effect, which is characterized by no side effects that can be seen on the skin of the rat's back.

Conclusion

In this research, it can be concluded that the variation of HPMC (Hydroxy Propyl Methyl Cellulose) concentration as a gelling agent in the preparation of ambon banana peel methanol extract gel affects the physical properties of the preparation which can be shown in the results of organoleptic testing, viscosity, and spreadability. The variation of HPMC (Hydroxy Propyl Methyl Cellulose) concentration as a gelling agent in the preparation of ambon banana peel methanol extract gel does not affect the irritationg effect on the skin which can be shown in the results of *in vivo* irritation testing on male wistar rats. The test result showed the absence of erythema (redness) and udema (swelling).

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