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paper text:

Design of Kaffir Lime Peel Extract Tablets by Direct Compression: Effects of Filler-Binder on Rheological Properties Wenny Irawaty^{1, a)}, Lannie Hadisoewignyo², Jenifer Wijaya¹, Shindy Saera Sababalat¹ and Andy Sebastian Tanjaya² ¹Chemical Engineering Department, Faculty of Engineering,

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wenny_i_s@yahoo.com Abstract. Dried kaffir lime peels from Citrus hystrix were extracted with ethanol by maceration method, followed by solvent evaporation to obtain dry extract. Due to economical aspect and

good flow properties of the extract, a direct compression method was applied in making the tablets. The main objective of this study was to study the influence of filler-binder (Avicel PH 102, Emcompress and Lactose) on rheological properties of kaffir lime peel extract tablet dough. Firstly, kaffir lime peel extract was prepared by peeling, cutting and drying kaffir lime peels prior to soaking them to ethanol. After separating the solid part, the extract was subsequently concentrated and filler was added into the crude extract to obtain dry product. Secondly, dry extract was then combined with filler-binder, sweetener and lubricant prior to the compression. Rheological properties evaluated in this study were density, flow time, the Carr index and the Hausner ratio. Thirdly, the best formulation dough was compressed to produce tablets. From the results, it can be concluded that ethanol is the best solvent to extract polyphenols from kaffir lime peels. In addition, the use of a mixture of lactose and Avicel PH 102 as the filler-binder agent exhibited the best formulation.

5INTRODUCTION Natural antioxidants from fruits offer an alternative source of dietary ingredients to promote healthy life.

In vivo studies show that epigallocatechin gallate contained in green tea is able to inhibit memory deficits in Alzheimer case [1], hesperidin isolated from citrus peels allows the regeneration of ulcerated tissue and prevents hemorrhagic injury of gastric mucosa [2], polyphenols in cocoa bean can reduce the risk of atherosclerosis [3], anthocyanins isolated from blueberry exhibits protection on liver [4], xanthenes in mangosteen can protect nervous system [5], flavonoids of polymethoxylated flavones, procyanidins and isoflavones tyrosinase in several extracts (tangerine peels, cocoa and red clover) is potent to treat Parkinson's disease [6], and so forth. Basically, the assessment on antioxidant activity of plant extracts has lately received great attention. Kaffir lime (*Citrus hystrix*) is selected in this study since the utilization of this fruit is still limited hence further investigation is required. Kaffir lime peels have been claimed to exhibit several activities, such as neutralize free radicals [7], antidiabetic performance [8], anti-inflammation action [9], and anti-microbial activity [10]. However, the use of kaffir lime peels is still limited, for instance, a certain amount of kaffir lime peel added in tea-based commercial drink to obtain citrus flavor. Therefore, further investigation to develop kaffir lime peels as advanced products becomes a challenge. Here, we investigate a possibility of kaffir lime peels extract to be processed as a tablet. Considering the benefits shown by kaffir lime peels, it is expected that the tablet can be a potential supplement to improve stamina and as an anti-degenerative agent.

**2Exploring Resources, Process and Design for Sustainable Urban Development AIP Conf. Proc. 2114, 020006 -1– 020006 -6;
<https://doi.org/10.1063/1.5112390> Published by AIP Publishing. 978-0-7354-1850-9/\$30.00**

Nowadays, tablet is still among the favorite forms of commercial drugs for treating diseases [11-13]. It has used to Carr's plant extract to be used as an anti-microbial agent, supplement and even as an anti-cancer agent [14-16]. Tablets are obtained from the aggregation of powder by applying pressure during the process. Direct compression method offers several advantages compared to other methods, e.g., granulation technique, since the method requires less cost, labor and time. Accordingly, direct compression method is widely applied in pharmaceutical industries. Efforts have been made to optimize the tablet formulation [17,

18]. Proper flowability of the materials is an important element to ensure rapid flow and dose uniformity during die-filling. In addition, compactability is also required to obtain satisfactory result since the materials must remain in compact form after the compression force is removed. The tablet generally consists of plant extract, filler, binder, sweetener, flavor, color, preservative and lubricant. Plant extract usually exhibits poor flowability in which this characteristic frequently becomes a problem during the preparation phase. Another factor is the hygroscopic property of tablet-forming materials since plant extract tends to be hygroscopic due to high affinity of the plant phytochemicals to water vapor present in the environment. Common sweetener added during tablet preparation is mannitol, sucrose, dextrose, saccharin, and so forth. However, some sweeteners exhibit hygroscopic characteristic, lack of stability in the presence of water, and bitter after taste. Therefore, this study aimed to formulate kaffir lime peels extract tablet by evaluating the effect of filler-binder on the rheological properties of the tablet dough, followed by tablet preparation through direct compression method. MATERIALS AND METHODS Materials Kaffir lime fruits were purchased from a local market in Surabaya, East Java. Different solvents (ethanol solution with concentrations of 96% and 41%) were employed to extract polyphenols compounds from kaffir lime peels. Magnesium aluminometasilicate (Neusilin US2) was added to the extract to obtain dry extract. Filler-binders used were

1 ?-lactose monohydrate (Lactose), dicalcium phosphate dehydrate (Emcompress), microcrystalline cellulose (Avicel

PH 102).

1 Distilled water and ethanol (96%) from commercial source were also used.

The sweeter was mannitol. Methods The methods include extract preparation, tablet powder characterization, tablet preparation and tablet characterization. Extract Preparation Fresh fruits were washed and rinsed with water to remove dirt and soil. Subsequently, they were peeled and cut into a size of 0.5 x 0.5cm. After that, the peels were dried under forced draft fan for 48 h. The peels were then soaked in ethanol (1: 40w/v) for 8 h at room temperature. After separating the solid part, the extract was concentrated by using a rotary vacuum evaporator (IKA, RV10) at 50oC followed by the addition of neusilin to obtain dry extract. Tablet Preparation The composition of tablet is shown in Table 1. Extract, filler-binder and mannitol

1 were blended for 5 min by tumbling

at 100 rpm (Erweka). Subsequently,

1 magnesium stearate was added and blended for another 2 min.

After that, the mixture was compressed to obtain the kaffir lime peel extract tablet. Characterization Prior to tablet preparation, the powder was characterized by measuring its moisture content, flow time, the Carr index and the Hausner ratio. The moisture content was measured by using moisture analyzer balance. Flow-time data were assessed by the bulk, and tapped densities were determined

3in a 100 -mL graduated cylinder mounted on a mechanical tapping device

(Erweka SVM12). Firstly, the sample was introduced into the cylinder until the reading reaches the 100 mL-mark and the total weigh was recorded. Then, it was tamped until a constant volume was obtained (around 500 times) and the

3final volume was documented. The **bulk density was calculated as the ratio between the sample weight and the initial volume.** The **tapped density was** obtained from **the ratio between the sample weight and the final volume. The**

evaluated rheological properties of powder are density, flow time and compressibility which the latter is expressed as the Carr index and the Hausner ratio. RESULTS AND DISCUSSION Tablet manufacturing by direct compression offers benefits compared to other methods. However, it is necessary to consider the properties of plant extracts added in the tablet mixture since it will determine the product characteristics, including flowability, compactability and compressibility. For the present study, kaffir lime peels extract was prepared by different solvents, followed by an evaluation prior to the compression method for tablet preparation. Previous study [19] shows the best solvent to extract polyphenols from kaffir lime peels is ethanol 41%, therefore, it was firstly selected as the extraction solvent in the present experiment. To investigate any possibility to use other solvents, ethanol solution with different concentrations, i.e. 70 and 96% were used and examined. After the concentration phase, kaffir lime peels extracts were obtained from different extraction solvents are shown in Fig. 1. FIGURE 1. The effect of solvent on the appearance of kaffir lime peel extract: (a) 41% ethanol, (b) 70% ethanol, and (c) 96% ethanol As demonstrated in Fig. 1, the solvents employed to extract polyphenols from kaffir lime peels influences the characteristics of the extracts. Figure 1(a) is the extract obtained from ethanol 41%. It was expected that the use of 41% ethanol will offer more benefits for tablet manufacturing since the extract contains the optimum polyphenols compounds of kaffir lime peels. Since 41% ethanol is used as the solvent, the extract solution contains a lot of water. Due to the restriction in the laboratory, in this experiment, the water cannot be removed completely. Even after the concentration period is prolonged, total duration for concentration phase is around 6 h, the extract cannot be further concentrated. After 6 h of heating process at 40oC, the citrus aroma on the extract cannot be identified. It indicates that the essential oil or compounds that were originally extracted from kaffir lime peels were vanished during the heating process even at low temperature. From the examination on the extract, it is obvious that it would be difficult to dry the extract and therefore, it cannot be further processed tablet preparation. Furthermore, 70% ethanol was selected as the solvent and the extraction steps were similar as before. Since the ethanol concentration was higher, it is easier to evaporate the ethanol. Similar to the case of 41% ethanol, the extract still contains water, but in lesser amount (Fig. 1(b)). Accordingly, the extract cannot be added to tablet ingredients since the tablet powder will be wet and cannot be pressed in the press machine. The use of 96% ethanol is another option to obtain dry extract regardless the type and composition of polyphenols being extracted from the peels. Since 96% ethanol is used as the solvent, it can be easily removed until it is almost dry and the color of the solution does not change during the process. However, it is noticeable that the concentrated extract is present in black tiny particles in the solution (Fig. 1(c)). We found those particles are polyphenols which initially dissolves in ethanol but later, some polyphenols cannot dissolve due to the availability of limited ethanol in the system. Subsequently, heating process is done on the solution, resulting dry extract of pure kaffir lime peels with a darker color final result.

For the preparation of kaffir lime peels extract tablet, the extract as shown in Fig. 1(c) is added to the tablet ingredients due to the color extract, and the result is examined. Therefore, another effort has been tried by applying short heating to the solution obtained by maceration method. Just before the black tiny particles formed in the solution, neusilin was added and the heating process was further continued until dry extract was obtained. The yield of extract was around 25%. Furthermore, dry and yellow yield was obtained as expected (Fig. 2). FIGURE 2. Kaffir lime peels in different forms: (a) crude extract solution, (b) dry extract, and (c) tablet Dry extract may not

1 exhibit the good rheology and compressibility required for tablet preparation **by direct compression**. Several attempts **have** been proposed **to**

improve the rheology properties of plant extracts and their dough tablets, such as extract drying method [20], the selection of suitable excipients during formulation [17, 21], operating conditions [21], and so forth. During the extract preparation, neusilin was added to obtain dry extract. It can be observed that the dry extract demonstrated suitable flowability (data is not provided). Dry extract of kaffir lime peels was further processed into tablet after they are mixed with other ingredients. The compositions of tablet have been investigated and the results are

1 shown in Table 1. The rheological properties of tablet powder **were evaluated,**

including moisture, flow time, density, the Carr index, and the

1 Hausner ratio. The **results are** tabulated **in Table 2.**

TABLE 1. The composition of kaffir lime peels extract tablet Composition Formula (%) I II III IV V VI Extract 24 19 15 15 60 60 54 54 Filler-binder (Avicel PH (Avicel PH 102) (Avicel PH 102) (Emcompress) 102) Mannitol 15 20 30 30 Magnesium 1 1 1 1 stearate 15 54 (Emcompress & Lactose 1:1) 30 1 15 54 (Avicel PH 102 & Lactose 1:1) 30 1 TABLE 2. The rheological properties of tablet dough Moisture (%) 6.1 6.2 6.1 2.1 1.8 4.0 Flow time ok ok ok x x ok Bulk density (g/mL) 0.4095 0.3812 0.3943 0.4536 0.4406 0.4072 Tapped density (g/mL) 0.4914 0.4530 0.4868 0.6630 0.6330 0.5312 Carr index (%) 16.7 15.8 19.00 31.6 30.4 23.3 Hausner ratio 1.20 1.19 1.23 1.46 1.44 1.30 I II III IV V VI Characteristic Formula As demonstrated in Table 2, the rheological properties of tablet powder are significantly affected by ingredients added into the mixture. The bulk and tapped density of the mixture added with Avicel PH 102 as the filler-binder were 0.40 and 0.45 g/mL, respectively. Accordingly, the values of Carr index and Hausner ratio are in the range of 16-19% and 1.2, respectively. The Carr index greater than 25 is considered to possess poor flowability. Therefore, the formula I to III of the tablet powders have good flowability. Mannitol is selected in the present study since it has a relatively low-calorie sweetener and poorly adsorbed in the small intestine, as well as it contains glycemic index of zero [23]. Therefore, the product will be suitable for people with diabetes. In addition, mannitol provides cooling effect to improve the taste and thus, enhance the acceptance level of the tablet by customers. However, mannitol is hygroscopic and the presence of mannitol may reduce the flowability property of the powder. Data presented in Table 1 shows formula I to III, which exhibit the good flowability of the powder. The comparison between formula III and IV indicates that the use of emcompress as the filler-

binder increases both bulk and tapped density by 15% and 36%, respectively. Emcompress consists of dicalcium phosphate dihydrate, high density material, making the mixture possesses a higher density compared to microcrystalline cellulose (Avicel PH 102) [17]. The moisture content, however, decreased by 67%. Meanwhile, β -lactose monohydrate is a relatively dry filler-binder compound. Therefore, the addition of lactose to Avicel PH 102 (1:1) has decreased the tapped density from 0.6630 to 0.6330 g/mL (compared to emcompress alone). Similar trend was observed for the bulk density as shown in Table 2. However, the parameter of Carr index of both formula IV and V, which is in the range of 30 and 32, indicates a poor flowability of the mixture. When emcompress (formula V) is replaced with Avicel PH 102 (formula VI), the density of the mixture is lower than the previous one. This finding verifies previous result that emcompress exhibits higher density material. Thus, the use of Avicel PH 102 decreased the tapped density in greater extent than the bulk density, as indicated by the decrease in the Hausner ratio from 1.44 to 1.3 or from 30 to 23 for the parameter of Carr index. Moreover, the moisture content decreased from 6.1% (filler-binder of pure Avicel PH 102; formula III) to 4.0 % (filler-binder of a mixture of Avicel PH 102 and lactose; formula VI), which is consistent with previous result. The Carr index has decreased to below 25, showing a good flowability of the powder in the system. Considering several parameters were observed during the preparation of kaffir lime peels extract tablet, the combination of Avicel PH 102 and lactose is the best filler-binder added during solid form formulation. Kaffir lime peels extract tablet prepared by direct compression method is shown in Fig. 2(c). CONCLUSION In the formulation of tablet from kaffir lime peels extract, there are several main conclusions. Firstly, the importance of solvent employed to extract polyphenols from the peels to accommodate the property of the produced extract. Since the tablet is prepared by direct compression method, thus the plant extract must be dry perfectly and it can be achieved by the use of ethanol as the solvent, followed by the addition of neusilin as the drying agent. The solid extract exhibits good flowability property. Secondly, filler-binder provides significant effect on the characteristics of the produced tablet. The best filler-binder evaluated in the present study is a combination of Avicel PH 102 and lactose.

4ACKNOWLEDGMENT This work was supported by the Directorate General of Higher Education, the Ministry of Education of Indonesia (RISTEKDIKTI) through Research Grant

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