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Original Article

LOZENGES FORMULATION OF CIPLUKAN (*PHYSALIS ANGULATA* L.) FRUIT EXTRACT AS AN ANTIOXIDANT WITH COMBINATION OF FILLER AGENTS AVICEL PH 102–LUDIPRESS

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ABSTRACT

Objective: This research aimed to determine the effect of variations in the concentration of filler agents Avicel PH 102-Ludipress on the evaluation results of granules and tablets and to determine the antioxidant activity of ciplukan (*Physalis angulata* L.) fruit extract lozenges.

Methods: The extract was obtained by the soxhletation method using ethanol 96%. The lozenges were made by direct compression, and the formula was divided into 3 concentration variations of Avicel PH 102 and Ludipress, namely F1 (1:2), F2 (1:1), and F3 (2:1). The best lozenges were tested for their antioxidant activity using the DPPH method.

Results: The results of statistical analysis using the One Way Anova test formulation of ciplukan fruit extract lozenges with variations in concentrations of Avicel PH 102 and Ludipress had a significant effect ($p<0.05$) on the angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, thickness, friability, and disintegration time, but no significant effect ($p>0.05$) on diameter, weight variation, and hardness. The best ciplukan fruit extract (F1) lozenge formula has a concentration ratio of Avicel PH 102 and Ludipress (1:2) with an IC_{50} value of 28.46 ppm and is classified as a very strong antioxidant.

Conclusion: Ciplukan fruit extract formulated in the form of lozenges with varying concentrations of the filler Avicel PH 102: Ludipress (1:2) has very strong antioxidant activity.

Keywords: Ciplukan fruit extract, Lozenges, Avicel PH 102, Ludipress, Antioxidant

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INTRODUCTION

Free radicals have an important role in tissue or cell damage. Free radicals can to penetrate human body tissue and disrupt the cells in question, resulting in them losing their desired function and structure. Free radicals in large enough quantities and through oxidative stress can cause cell damage. This cell damage can result in various chronic and degenerative diseases. Excessive free radicals can be prevented and neutralized with compounds called antioxidants [1].

Antioxidants function to neutralize free radicals, which can prevent damage to the body by completing the lack of electrons in these free radicals [2]. Antioxidants are compounds that can protect cells from the dangers of reactive oxygen free radicals. Antioxidants based on their sources are classified into two, namely synthetic antioxidants and natural antioxidants [3].

Natural antioxidants which are commonly found in plants such as vegetables or fruit, generally have compounds containing phenolics or polyphenolics in the form of flavonoids, and their derivatives include cinnamic acid, coumarin, tocopherol, and polyfunctional acids. Secondary metabolites that are antioxidants include alkaloids, flavonoids, polyphenols, phenolic compounds, steroids, and terpenoids. Flavones, flavonols, flavanols, isoflavones, catechins, and chalcones are part of the flavonoid group which has antioxidant activity. One plant that can be used as a source of natural antioxidants is the ciplukan (*Physalis angulata* L.) [4].

Based on research conducted by Nuranda (2016), it is stated that ciplukan fruit extract has antioxidant activity with an IC_{50} value of 63.46 ppm, which shows that ciplukan fruit extract has the potential as a strong antioxidant. Efforts can be made to make an antioxidant preparation that is more practical and easier to consume in the form of a lozenge tablet [5].

Lozenges have several advantages, including being easy to consume, having a good taste, increasing the patient's ability to receive medication, and faster drug absorption. It is hoped that the ciplukan fruit extract lozenges can provide a faster effect to meet the needs of antioxidants in the body [5, 6].

Ciplukan fruit extract is not resistant to heating at temperatures above 60 °C, therefore, the direct compression method is the right way to produce ciplukan fruit extract tablets. One of the important excipients to be added to direct compressed tablet formulations is those that function as filler-binders [7].

The filler substances chosen in this study were Avicel PH 102 and Ludipress. Avicel PH 102 has the advantages of good flowability and compactibility, while Ludipress has the advantages of good flowability and encapsulation, low friability, and fast disintegration time, so it will produce good lozenges [8].

Based on the above background, the authors are interested in researching the formulation and evaluation of lozenges from ciplukan fruit extract (*Physalis angulata* L.) with varying concentrations of avicel PH 102 and Ludipress using the direct compression method. It is hoped that this research can increase the utilization of natural resources in Indonesia.

MATERIALS AND METHODS

Materials

Ciplukan fruit comes from plantations in the Ciwidey region of West Java, Indonesia. Povidon K-30 was pharmaceutical grade from Huangshan Bonsun Pharmaceutical Co. Ltd, China. Avicel PH 102 from Asehi KASEI, Japan. Ludipress was pharmaceutical grade from BASF, Germany. Sucralose was pharmaceutical grade from Anhui Jinhe Industrial Co. Ltd, China. Orange flavor from PT. Firmenich, Bogor, Indonesia. Colloidal silicon dioxide and magnesium stearate were pharmaceutical grade from Faci Asia Pacific PTE LTD, Singapore. DPPH from Sigma Aldrich, USA.

Extraction of ciplukan fruit

Ciplukan fruit extract (*Physalis angulata* L.) was obtained by the soxhletation method for 8 h and using 96% solvent [9].

Preparation of lozenges (Direct compression)

In this research, 3 formulas lozenges of ciplukan fruit extract were made with varying concentrations of avicel PH 102 and Ludipress as fillers, respectively F1 (1:2), F2 (1:1), and F3 (2:1). The composition of the lozenges is shown in table 1. Lozenges are prepared by direct compression method. All ingredients are prepared and weighed. Ciplukan fruit extract was mixed with colloidal silicon dioxide. Avicel PH 102 was added until the mixture was dry, then sieved with mesh number 40 (mixture 1). Ludipress was added to mixture 1 until homogeneous. Povidone K-30, sucralose, and orange flavoring were mixed until homogeneous for 3 min (mixture 2). Mixtures 1 and 2 were mixed until homogeneous. Magnesium stearate was added as a lubricant agent, and then the mixture was compressed with a tablet compression machine [10, 11].

Table 1: Formula lozenges of ciplukan fruit extract

Ingredients	Formula (%)			Function
	F1	F2	F3	
Ciplukan Fruit Extract	15	15	15	Active ingredient
Povidone K-30	2.5	2.5	2.5	Binder
Avicel PH 102	25	37.5	50	Filler
Ludipress	50	37.5	25	Filler
Orange Flavor	3.45	3.45	3.5	Flavour
Sucralose	0.05	0.05	0.05	Sweetener
Colloidal silicon dioxide	2	2	2	Adsorbent
Magnesium stearate	2	2	2	Lubricant

Evaluation of pre-compression parameters

Angle of repose

The frictional force on the powder can be measured by the angle of repose. It is defined as the maximum possible angle between the surface of the powder pile and the horizontal plane [12]. To determine the Angle of Rest, the powder is passed through a funnel that is aligned vertically, and the height (h) and radius (r) of the pile formed is determined and the angle of rest is calculated using the following formula [13].

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1}[\frac{h}{r}]$$

Where θ is the angle of repose, "h" is the height in cm, and "r" is the radius in cm.

Bulk density

A total of 20 g of granules was put into a 100 ml measuring cup. The measuring cup was tapped twice with an interval of 2 seconds using a bulk density apparatus. Bulk density is calculated using the following formula [12].

$$\text{Bulk density} = \frac{\text{Weight of powder initial}}{\text{Bulk volume of granule}}$$

Tapped density

Tapped density is obtained using granules as much as 20 g mechanically tapped graduated measuring cylinder using a bulk density apparatus until a constant volume is followed by calculation using the following formula [13].

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of granule}}$$

Carr's index

Carr's compressibility index was used to calculate the granule compressibility index. It is a test that easily determines bulk density, tapped density, and granule agglomeration rate. The following formula is used to calculate the Carr's Index [14].

$$\text{Carr's index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \text{x}100$$

Hausner's ratio

Hausner found that the ratio of tapping density/bulk density is related to the friction between the particles so that it can be used to predict the flow properties of granules [15].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of post-compression parameters

Weight variation

A total of 20 tablets were taken and weighed one by one on an analytical balance. Then the results are recorded and the average is calculated, followed by calculating the standard deviation of each tablet from the average weight. Not more than two individual weights differ from the average weight by more than 5% and neither by more than 10% [13].

Thickness and diameter

A total of 20 tablets were measured in diameter and thickness using a micrometer and thickness tester [16].

Hardness

A Monsanto Hardness Tester measured the hardness of the prepared tablets. The tablet was placed between two anvils; the force applied to the anvils and the crushing strength that caused the tablet to break was recorded [13].

Friability

Twenty tablets were randomly selected and weighed. The tablet was tested for friability using a friabilator (Roche type) for 100 revolutions (25 rpm for 4 min). The tablet is removed from the device, then de-dusted and weighed again. Average Triplicate readings were noted and calculated [17].

$$\%F = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \text{ X } 100$$

Disintegration time

The time taken by the lozenges to dissolve completely was determined by USP disintegration apparatus, where lozenges were placed in each tube of the apparatus and the time taken for the lozenges to dissolve completely was noted by using 900 ml phosphate buffer of pH 6.8 at 37 °C. This test was done in triplicate. The average dissolving time for lozenges was calculated [18].

Antioxidant activity test

Antioxidant tests were carried out on lozenges of ciplukan fruit extract using the DPPH method. The formula tested for antioxidants is the best formula based on the results of the physical evaluation that has been carried out. A total of 1 mg DPPH was dissolved in 96% pa ethanol to a concentration of 20 ppm [19]. One lozenge was crushed and weighed until it was equivalent to 3 mg of extract, then dissolved in 96% pa ethanol and varied. Concentrations of 10, 30, 60, 90, and 120 ppm 120 ppm [20]. The samples were incubated at 37 °C for 60 min and then the absorbance was measured using a UV-Vis spectrophotometer at a wavelength of 517 nm. Free radical scavenging activity was calculated as the percentage reduction in DPPH color using the inhibition measurement equation. Next, the %inhibition is plotted against each concentration used and from the graph, the IC_{50} value can be calculated [21].

Statistical analysis

Statistical analysis was carried out using the one-way analysis of variance (ANOVA) method. If the data is not normally distributed, then the Kruskal-Wallis analysis method is used to investigate the

effect of variations in filler concentration on the evaluation of lozenges [21, 22].

RESULTS AND DISCUSSION

Characterization of pre-compression parameters

Angle of repose

An easy characteristic to measure that provides an approximation of the cohesive behavior of powders is the angle of repose. Based on table 2, the results of the angle of repose evaluation show that F1 and F2 have excellent flowability; meanwhile, F3 has good flowability. Characterization of the flow ability of a powder based on the angle of repose is classified as excellent (<25˚), good (25˚-30˚), moderate flow (30˚-40˚), poor flow (>40˚) [23]. The smallest angle of repose is at F1, due to the largest Ludipress concentration. Ludipress has good flow properties, so the greater the concentration of Ludipress used, the smaller the angle of repose formed [24].

Bulk density

The apparent bulk densities for all formulated batches were found to be between 0.401±0.008 g/ml and 0.548±0.007 g/ml. Bulk densities were found within acceptable limits, which indicates that the packing properties required during compression are adequate in all formulations [12].

Tapped density

The values of tapped density were found to be between 0.463±0.001 g/ml and 0.636±0.009 g/ml. Tap densities were found within acceptable limit, which indicates that the packing properties required during compression are adequate in all formulations [12].

Carr's index

Based on the research results, Carr's index values for the three formulas were included in the excellent flow category in the range of 5-15%. The relationship between powder flowability and compressibility value is excellent flow (5-15%), good (16-18%), fair (19-21%), poor 22-35%), very poor (36-40%), extremely poor (>40%) [25]. Formula F1 has the best compressibility value compared to F2 and F3, namely with a value of 9.8%. F1 has the best compressibility value due to the greater concentration of Ludipress used. Ludipress has the advantage of improving compressibility, so the greater the concentration of Ludipress used, the better the compressibility value produced [24].

Hausner's ratio

Flow property was also insured by measuring Hausner's ratio. The Hausner's ratio results from the three formulas are classified as good flow (1.106±0.013 to 1.161±0.031), where the value of less than 1.25. The relationship between Hausner's ratio value and powder flowability is that a value less than 1.25 indicates good flow and a value greater than 1.5 indicates poor flow [26].

Table 2: **Result of pre-compression parameters (n=3)**

No	Parameters	F1	F2	F3
1	Angle of repose (˚)	23.53±0.57	24.81±0.44	25.43±0.15
2	Bulk density (g/ml)	0.514±0.005	0.401±0.008	0.548±0.007
3	Tapped density (g/ml)	0.568±0.001	0.463±0.001	0.636±0.009
4	Carr's index (%)	9.8±0.001	13.35±0.016	13.85±0.024
5	Hausner's ratio	1.106±0.013	1.154±0.021	1.161±0.031

Characterization of post-compression parameters

Weight variation

The results of the evaluation of weight uniformity based on table 3 show that there is not a single tablet whose weight deviates from the weight range of 5% or 10%. The desired tablet weight in 1 tablet is 1500 mg, and the 5% range requirement of the average weight is 1425-1575 mg, while the 10% range requirement of the average weight is 1350-1650 mg [27].

Thickness and diameter

The mean thicknesses of all the formulations, F1 to F3 were found to be in the range of. 5.770 to 5.862 mm and the tablet mean diameter of all formulations was found to be in the range of 17.179 to 17.250 mm. This indicated that the tablet production was consistent and reproducible [18].

Hardness

The hardness evaluation results in table 3 show that F1, F2, and F3 have good tablet hardness. F1 has a relatively constant hardness result compared to F2 and F3. This is because the concentration of Ludipress F1 is greater than F2 and F3, making the tablet mass compact during the compression process. Ludipress has the property of improving the flow properties of a mixture of materials and is a co-processed material whose hardness results are not affected by machine speed and pressure, so it can produce tablets with relatively more constant hardness [24].

Friability

Based on table 3, the friability of the three formulas meets the requirements. The smallest F1 friability value is 0.02%, indicating that varying the Ludipress concentration influences tablet fragility namely the greater the Ludipress concentration used, the smaller the resulting friability [28].

Disintegration time

The evaluation results show that F1, F2, and F3 have disintegration times that meet the requirements. F1 has a faster disintegration time compared to F2 and F3 because the Ludipress concentration affects the resulting dissolution time; the greater the Ludipress concentration used, the faster the resulting dissolution time [7].

Table 3: Result of post-compression parameters

No	Parameters	F1	F2	F3	Acceptable criteria
1	Thickness (mm)	5.862	5.770	5.808	4/3 thickness<diameter<3 thickness
2	Diameter (mm)	17.250	17.179	17.198	
3	Hardness (kg/cm^2)	11.195	10.450	10.415	10-20
4	Friability (%)	0.02	0.12	0.13	<1
5	Disintegration time (minute)	9.03	9.97	13.13	<30

Antioxidant activity test

The antioxidant activity test was carried out on the best formula, namely F1, with a ratio of Avicel PH 102 and Ludipress (1:2). According to Molyneux (2004) it is known that a compound is said to be a very strong antioxidant if the IC_{50} is less than a value of less than 50 ppm (IC_{50}<50 ppm), strong (50 ppm<IC_{50}<100 ppm), moderate (100 ppm<IC_{50}<150 ppm), weak (150 ppm<IC_{50}<200

ppm), and very weak (IC_{50}>200 ppm). The results of the antioxidant activity test on ciplukan fruit extract lozenges using the DPPH method showed an IC_{50} value of 28.46 ppm and had very strong antioxidant activity [29].

Table 4: Concentration, inhibition percentage, and IC_{50} of ciplukan fruit extract lozenges (n=3) (mean±SD)

Concentration (ppm)	Inhibition percentage (%)	IC_{50} (ppm)
10	73.90±0.0024	28.46
30	64.63±0.0037	
60	53.90±0.0024	
90	60.48±0.0028	
120	54.85±0.0014	

Statistical analysis

The normality test showed that distributed data was not normal ($p<0.05$), then continued with the Kruskal-Wallis test. Statistical analysis using the Kruskal Wallis Method to investigate the effect of variation in the concentration of filler on the evaluation results of lozenges. Variations in the concentration of filler in the lozenges had a significant effect ($p<0.05$) on angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, thickness, friability and disintegration time, and had no significant effect ($p>0.05$) on diameter, weight variation and hardness [21].

CONCLUSION

Ciplukan fruit extract formulated in the form of lozenges with varying concentrations of the filler Avicel PH 102: Ludipress (1:2) has the best physical properties (pre-compression and post-compression parameters) and very strong antioxidant activity (IC_{50} 28.46 ppm).

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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