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Influence of croscarmellose in fast disintegrating tablet of *Syzygium polyanthum* extract

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ABSTRACT

Bay leaves (*Syzygium polyanthum*) contain the flavonoid quercetin which can be used as an antihyperlipidemic drug. The development of antihyperlipidemic drug formula in the form of fast disintegrating tablet (FDT) is needed for patients who experience dysphagia. FDT preparations require an optimal super disintegrant concentration to produce a good drug formula. This study aims to develop the FDT formula of bay leaves extract using the super disintegrant croscarmellose sodium (CCS) intra and extra-granular. FDT formulation using the wet granulation method with variations of CCS concentrations; F1: 2%, F2: 3.5%, and F3: 5% for extra granular, and 2% for intra granular. The formulation process, in-process control (IPC) granules, weight uniformity test and various physical properties tests of tablets were carried out. Data were statistically analyzed using one way ANOVA test (α=95%). The results of statistical tests of IPC granules, uniformity of weight, and tablet size of all FDT formulas were not significantly different ($p>0.05$). The CCS concentration for extra granular significantly affected the wetting time, disintegration time, hardness, and the value of friability percentage of FDT ($p<0.05$). The combination of intra and extra-granular CCS (2%:5%) gave the most optimum physical properties of bay leaf extract FDT.

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1. INTRODUCTION

Plant germplasm resources are raw materials for medicines, one of which is a bay leaf (*Syzygium polyanthum*). Bay leaves are known to contain secondary metabolites, such as saponins, terpenoids, flavonoids (quercetin), polyphenols, alkaloids, steroids, and essential oils (sesquiterpenes)[1]-[2]. Based on the Decree of the Minister of Health of the Republic of Indonesia (2009), bay leaves contain a total flavonoid of not less than 0.40% which is calculated as quercetin [3]. Quercetin in bay leaves the potential as an antihyperlipidemic which can significantly reduce levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol in plasma and tissues in hyperlipidemic rats with a parallel increase in high-density lipoprotein (HDL), as well as inhibiting 3-hidroksi-3-metilglutaril coenzyme A (HMG-CoA), reductase, and LDL oxidation [4].

Conventional drugs for hyperlipidemia are generally available in tablet form. However, the tablet dosage form has several disadvantages. Some of them require a long absorption time in the body, and slow drug action, and elderly patients may experience difficulty swallowing or dysphagia [5]. Seeing the problems that arise from conventional tablets, the herbal fast disintegrating tablet (FDT) of bay leaf extract is the right alternative so that the drug can be used comfortably and has a therapeutic effect more quickly. FDT is a solid

dosage form containing pharmaceutically active substances that can be disintegrated quickly, generally within seconds when placed in the tongue. This properties of FDT can release the active drug substance immediately, speed up the onset, increase the oral bioavailability of the drug in the body so that therapeutic effectiveness can be achieved [6]-[7]. FDT preparations combine two advantages of preparations, namely liquid which can increase the solubility and bioavailability of drugs, as well as the advantages of solid dosage forms that have high physicochemical stability, relatively constant homogeneity of the active ingredients of the preparation, and easier manufacturing.

FDT is formulated with croscarmellose sodium (CCS) super disintegrant which is classified as a strong swelling product with a good water absorption mechanism [7]-[8]. CCS is effectively used in FDT preparations because it rapidly expands to 4-8 times its initial volume when in contact with water, thus accelerating the tablet-crushing process. CCS is effective intra-granular which allows for better capillary and swelling processes, causing the tablet to disintegrate quickly and reduce disintegration time [8]. The addition of intra and extra-granular crushing materials can increase the effectiveness of tablet disintegration through two stages, i) extra granular which breaks the tablet into granules, and ii) intra granular breaks down the granules into smaller particles. The mechanism is crushing material that experiences rapid swelling and water absorption (wicking) through the gaps between the granules and the particles that make up the granules [9]. This study aims to develop herbal FDT with the active ingredient of bay leaf ethanol extract. The concentration of CCS super disintegrant intra and extra-granular needs to be determined to obtain the FDT of bay leaf extract with optimum physical properties.

2. METHOD

The ingredients used were bay leaf extract in the form of fresh bay leaf collected from tradisional market, Beringharjo market, Yogyakarta, Indonesia, ethanol 70%, croscarmellose sodium (PT. Phapros Tbk), lactose, magnesium stearate, aspartame, menthol and corn starch paste (pharmaceutical grade). The tools for extraction used are oven, rotary evaporator calipers, waterbath, vacuum pump. The tools for granule physical properties test used are Ohaus analytical balance, absorption test equipment granules, volumenometer (tapped density tester), flow tester granule, sieving machine, dry granule sieve, wet granule sieve, pan, halogen moisture analyzer. the tools for tablet test used are single punch tablet printing machine, hardness tester, friability tester, and disintegration tester.

2.1. Bay leaf ethanol extract

Bay leaves were dried in an oven at 50-60°C until a moisture content of less than 10% was obtained. Simplicia were extracted by maceration method using 70% ethanol solvent (1:10) (w/v) [3]. Maserati and pulp were separated by the vacuum pump and filter paper. The solvent was evaporated using a rotary evaporator. The viscous extract obtained was calculated for its yield.

2.2. FDT formulation of bay leaf extract

FDT was made by the wet granulation method. At the granulation stage, bay leaves extract was mixed with intra granular CCS, lactose and corn starch. The mixture was sieved through a wet (no. 18 mesh), oven-dried (50-60ºC), then sifted dry (no. 20 mesh). The granules and excipients consisting of magnesium stearate, aspartame, menthol, and CCS (extra granular) mixed until homogeneous (30 minutes). Mixture of granules and excipients that have been homogenized are compressed using a single punch tablet press.

2.3. Granule physical properties test parameters

The moisture content of granules can be determined based on the value of loss on drying (LOD) and MC. LOD is a test for measuring the difference in heavy total granules when before and after drying or a moisture content statement based on wet weight. Meanwhile, MC is a statement of moisture content based on dry weight. Measurements using the halogen moisture analyzer tool. Good granule moisture content if the LOD and MC values are 10% [10].

The flow properties of the granules can be tested by calculating the angle of repose, the flow time test, and the determination index (Hausner ratio). The granule angle of repose α (degree) is said to be very good (25º-30º); good (30-35º) or 25º><35º. A good granule flow time is not more than 10 seconds for 100 grams of granules [11]. Excellent granule setting index (≤10); good (11–15), and the Hausner ratio index that meets the requirements for the physical properties of the granule mass, which is very good (1.00–1.11); good (1.12–1.18).

Sieve no. 14, 16, 20, 30, 50 mesh and pan, installed in stages on the sieving machine (50 amplitude, 15 minutes). The granules left on each sieve were weighed and the percentage was calculated [10]. The fragility of the granules is based on the number of fines that occur after the friability test by sieving. The granules were put into a graded sieve with the top sieve no. 30 mesh and bottom pan, using a sieving machine (50 amplitude,

30 minutes). The water absorption of the granules affects the tablet's disintegration time (disintegration). It was carried out with a series of absorption test equipment by placing 300 mg of granules on a water-saturated sheath paper. The absorbed water was measured using a digital scale for 15 minutes or until it was constant [7].

2.4. Physical properties test parameters of FDT

Requirements and weight uniformity tests are determined based on the regulation of the National Food and Drug Agency of the Republic of Indonesia concerning the quality requirements of traditional medicines. The test was carried out by weighing 20 tablets one by one, from 20 tablets no more than 2 tablets, each of which deviated from the average weight by more than 5% and not one tablet whose weight deviated from the average weight. the average is greater than 10% [12].

Each tablet was measured in diameter in a horizontal position with a caliper, and the thickness of the tablet was measured in a vertical position with a caliper (millimeters). The tablet hardness test was carried out by taking a sample of at least 6 tablets from each formula. The tablet hardness test is carried out using hardness tester tablets. One by one the tablets are tested by placing the tablets in the center perpendicular to the hardness tester. A good FDT hardness is 3-5 kg/cm² [11], [13].

For tablets with a single weight of exactly or less than 650 mg, the total weight of the tested samples was close to 6.5 grams. Prior to testing, the tablets were dusted and weighed. All tablets were put into the friability tester (speed 25 rpm, 4 minutes). The tablets were cleaned of adhering fines and re-weighed. A good friability value should not be more than 1% [11].

The wetting time test was done by placing a sheet of filter paper that has been folded twice into a petri dish with a diameter of 5 cm. The petri dish was filled with 5.0 mL of distilled water containing the strawberry red dye. A tablet is then placed on the filter paper, and simultaneously with the start of the test instrument, the stopwatch is turned on. Wetting time was calculated as the time required for a red color to appear on the entire surface of the tablet [14]. A total of 6 tablets of each formula were placed in each tube and a disk was placed on it, the test was carried out with water medium at a temperature of 37±2 °C or 35-39 °C using a 1000 ml glass beaker. The disintegration time requirement for FDT preparations is at least <1 minute disintegration time [11], [15].

2.5. Data analysis

The results of the physical examination of granules and tablets of FDT bay leaf extract were analyzed using the one-way ANOVA test method with a 95% confidence level.

3. RESULTS AND DISCUSSION

Bay leaf simplicia was tested for macroscopic (organoleptic) specifications on fresh and dried simplicia, as well as microscopic tests for simplicia parts and identification fragments of simplicia powder. Fragments prepared by dissolving in chloralhydrate and water [16]. The simplicia specification test was carried out to ensure the correctness of the identity and quality of the bay leaf simplicia based on the Indonesian Herbal Pharmacopoeia compendia and Indonesian Materia Medika. Based on the microscopic test results on Figure 1 there are identifier fragments namely i) lower epidermis with stomata, ii) upper epidermis, iii) elements with dots, iv) prism-shaped calcium oxalate crystals, and v) sclerenchyma. The results of the specification test for the simplicia of bay leaves showed that the simplicia used met the requirements of organoleptic and microscopic terms. The determination test of bay leaf simplicia at the Biology Laboratory of Universitas Ahmad Dahlan (UAD) was carried out to ensure that the selected bay leaf simplicia was in accordance with its species or identity [3], [17].

3.1. Extraction bay leaf

Fresh simplicia of bay leaves were sorted wet, dried using an oven (50-60ºC) with a moisture content of not more than 10%, then sorted dry. Simplicia powder for extract preparation is a fine simplicial (No. 60 mesh) in order to optimize the extraction process [18]. The results of the simplicial extraction of bay leaves weighing 3.7 kg obtained a thick extract of 347 grams. The total yield of the thick extract obtained was 9.38%. The morphology of the viscous extract is shown in Figure 2. Screening and determination of the chemical compound flavonoid quercetin contained in the thick extract of bay leaves was carried out at the Integrated Research Laboratory of the Faculty of Pharmacy, UAD. According to the Ministry of Health (2017), bay leaves contain a total flavonoid of not less than 0.40% calculated as quercetin. Based on the results of the test the flavonoid content of 0.8079±0.0045%, so that it meets the specifications for the total flavonoid content of bay leaves[17]. Quercetin is an active substance that has medicinal effects such as antiherlipidemia, antibacterial, antidiabetic, antioxidant [18], [19].

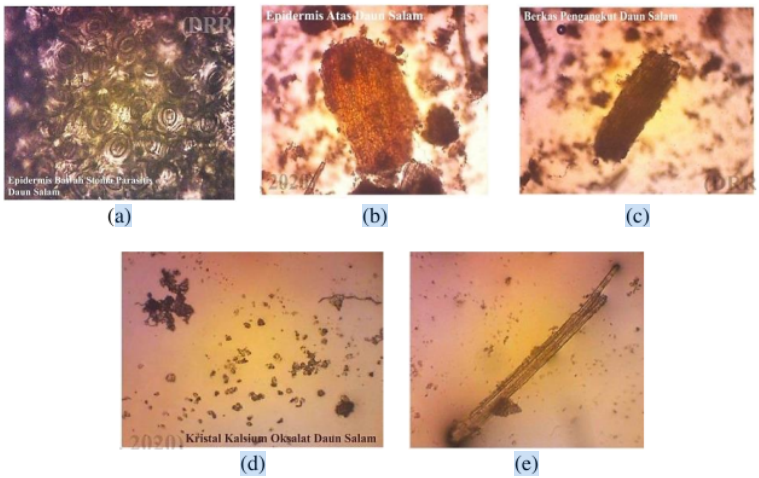

Figure 1. Identification fragments of bay leaf; (a) lower epidermis, (b) upper epidermis, (c) floem, (d) calcium oxalate crystal, (e) sclerenchyma

Figure 2. Bay leaf extract

3.2. FDT formulation

FDT formulation method with wet granulation is good used for water-resistant active ingredients and heating temperature [10]. The active ingredient in bay leaves quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonoid derivative compound that is resistant to heating with a melting point of 316.5 °C [20], while the wet granulation process ranges from at a temperature of 40-60 °C. The wet granulation method can improve the flowability and compatibility of the material and facilitate the FDT formulation process from the active ingredient in the form of a thick extract [21]. Wet granulation has the advantage of good content distribution and uniformity, besides that the hydrophobic surface of the tablet becomes more hydrophilic which affects the water absorption process into the tablet, thereby increasing the speed of tablet disintegration [22]. The work of woven fibers between granules can increase the speed of tablet disintegration[23], it is synergistic with the presence of CCS super disintegrant extra granular which facilitates swelling and absorption of water into granules and their small particles.

The concentration of CCS super disintegrant intra-granular of the three formulas was the same, 2% (10 mg/tablet), and extra granular was formulated with varying levels, F1 2% (10), F2 3.5% (17.5), and F3 5% (25 mg/tablet). The FDT formula for bay leaf extract is shown in Table 1. Based on the Handbook of pharmaceutical excipients the use of CCS in the wet granulation process should be added in the wet or granulation (intra-granular) stage, as well as in the dry (extra-granular) process [21]. Because this method can increase the wicking ability (water absorption) and swelling of the CCS super disintegrant.[8]

Table 1. Formula of FDT bay leaf extract

Ingredient	Composition (mg)		
	F1	F2	F3
Bay leaf extract	70	70	70
Croscarmellose sodium (intra granular)	10	10	10
Lactose	380	14	366
Croscarmellose sodium (extra granular)	10	17.5	25
Magnesium stearate	5	5	5
Aspartame	20	20	20
Menthol	41	1	1
Corn starch paste 5% w/v	qs	qs	qs
Total weight (mg)	500	500	500

3.2.1. Granule physical properties test parameters

One of the most crucial elements of wet granulation is the water content, MC and LOD has been was measured and the values of granules from all formulas as shown in Table 2, the results obtained meet the requirements of 32% ($p>0.05$). Water content will affect granule characteristics, including granule size and compressibility. The flow properties of the granules show the results of the angle of repose of the granules ranging from 30-35 (good), granule flow time of 10-14 grams/second (good), and the determination test/Hausner ratio (very good). The flow properties of granules are very influential on the tablet compression process, granules with good flow properties will cause the granules to enter the die space to be relatively constant so that the tablet weights with small weight variations can be obtained and can increase the uniformity of the resulting tablet dosage [8], [24], [25].

The average diameter of all granules ranged from 650-700 m ($p>0.05$) and the value of friability percentage of the granules ranged from 0.5-0.9% ($p>0.05$)[13]. The granule absorption test for all formulas had absorption between 0.120-0.190 mg/minute ($p>0.05$). The granule absorption shows the speed of the granules in absorbing water to crush the granules into small particles so as to speed up the tablet disintegration time. All in process control (IPC) granule parameters have met the requirements so that the tableting process can be continued with a single punch tablet press with a punch pressure of 13 kg.

Table 2. Results of examination of physical properties of FDT granules of bay leaf extract

Test parameters	Formula		
	F1	F2	F3
LOD±SD (%)*	7.03±0.76	6.29±1.28	6.57±1.18
MC±SD (%)*	2.98±0.17	2.35±0.33	2.69±0.31
Angle of repose±SD (°)*	30.66±1.75	31.18±2.92	30.08±2.30
Flow time±SD (grams/second)*	12.98±1.28	13.12±0.89	11.85±0.48
Assignment±SD (%)*	3.17±1.04	2.83±1.04	3.83±0.76
Hausner ratio Index±SD*	1.03±0.01	1.03±0.01	1.04±0.01
Average diameter±SD (μm)*	694.64±28.87	657.58±39.65	698.14±26.09
Fragility±SD (%)*	0.8028±0.20	0.8199±0.05	0.5863±0.04
Absorption±SD (mg/min)*	0.186±0.05	0.188±0.05	0.127±0.01

Note: (*) sig value. ($p>0.05$) means that the three formulas are not significantly different

3.2.2. Physical properties test parameters of FDT

The uniformity of tablet weight is related to the uniformity of active substance levels and therapeutic effects. The uniformity of tablet weight (Table 3) can be seen from the coefficient of variation F1, F2, and F3 all <5%, (0.0942, 0.1246, and 0.2103) %, respectively. The weight uniformity test based on the National Food and Drug Agency of the Republic of Indonesia requirements, shows the results that meet the requirements, where the tablet meets the specified weight deviation limit value range.

Hardness ranges FDT be good tablet from 3-5 kg/cm^2 [13], while the conventional tablet, is 4-8 kg/cm^2. The FDT hardness as shown in Table 3 shows results that mee 20 e requirements. Hardness affects the brittleness and disintegration time of tablets, as well as the dissolution/release of the active drug substance [8]. The results of statistical analysis of tablet hardness with sig. ($p<0.05$) indicates that the hardness of the three FDT formulas is significantly different. The hardness of FDT tablets is strongly influenced by the CCS super disintegrant excipient. FDT (F3) produced the hardest tablet with the highest extra-granular CCS concentration (5%), causing the particles in the tablet to be tightly bound. Croscarmellose sodium (Ac-Di-Sol) is a super disintegrant with a fibrous cross-linked polymer structure that functions as a disintegrant with a strong swelling mechanism, fiber is able to bind strongly to the particles so as to increase the hardness and reduce the brittleness of the tablet [26]. This causes the tablet to have good compatibility, so there is a tendency

to increase hardness as the amount of CCS in the tablet increases [27]. Another factor that affects the hardness of FDT is the upper punch pressure during the tableting process, the greater the pressure used, the harder the FDT will be. The results of the diameter and thickness measurements of the tablets showed that the size of the entire tablet was uniform (homogeneous).

The friability value of the tablet is based on the requirements, which should not be more than 1% [11]. The fragility value of FDT is shown in Table 3 with a friability value of <1% so that FDT meets the requirements. The results of the tablet friability statistical test have a sig. value ($p < 0.05$) means that the fragility value between formulas is significantly different. CCS super disintegrant is a factor influencing fragility. Formula 3 with the highest number of CCS has the smallest friability value, where there is a tendency to decrease the friability value as the number of CCS in the tablet increases. The friability value is inversely proportional to the tablet's hardness, where the harder a tablet is, the smaller the friability value will be.

FDT wetting time is shown in Table 3, FDT (F3) with the highest number of CCS has the smallest wetting time. Wetting time is a parameter to determine the speed of FDT in absorbing water, which affects the speed of tablet disintegration. The faster the wetting time, the faster the tablet disintegration. The wetting time of tablets is influenced by the structure of the tablet matrix and the hydrophilicity of the excipients [28]. The result of statistical analysis of FDT wetting time has a sig. value ($p<0.05$) means that the formulas differ significantly. FDT (F3) with the highest number of CCS had the fastest time for wettable tablets, super disintegrant CCS being the most influential factor. The cross-linked chemical structure of CCS creates excipients that have hydrophilic properties and very easy-to-absorb solvents resulting in outstanding swelling properties in the disintegration process.

Table 3. Results of examination of physical properties of bay leaf extract FDT tablets

Test Parameters	Formula			Note.
	F1	F2	F3	
Weight uniformity±SD (mg)	50 4.42±0.48	50 4.78±0.63	50 4.43±1.06	Appropriate*
Diameter±SD (mm)	12.00±0.00	12.00±0.00	12.00±0.00	Appropriate*
Thickness±SD (mm)	3.67±0.00	3.67±0.00	3.68±0.01	Appropriate*
Hardness±SD (kg)	4.46±0.25[c]	4.50±0.27[c]	5.24±0.32[a,b]	In accordance
Fragility±SD (%)	0.77±0.05[c]	0.72±0.04[c]	0.52±0.04[a,b]	In accordance
Wetting time±SD (seconds)	50.33±3.06[c]	43.33±4.04[c]	20.00±2.65[a,b]	In accordance
Disintegration time±SD (seconds)	45.33±5.86[c]	38.33±3.79[c]	19.67±3.06[a,b]	In accordance

Note: (*) sig value. ($p>0.05$) means that the three formulas are not significantly different
(a) means a formula that is significantly different from the formula 1
(b) means a formula that is significantly different from the formula 2
(c) means a formula that is significantly different from formula 3
F1: CCS intra granular 2%: extra granular 2%
F2: CCS intra granular 2%: extra granular 3.5%
F3: CCS intra granular 2%: extra granular 5%

Disintegration (disintegration) time FDT has at least a disintegration time of less than 1 minute [15]. Another source says that in-vitro about 30 seconds or less [29], whereas according to Ph. euros. is <3 min in the oral cavity before swallowing [29], [30]. The faster disintegration time will increase the speed of drug release from the tablet which affects the effectiveness of therapy. The results of the disintegration time of FDT in table 3 show that it meets the requirements of the disintegration time of FDT (<1 minute). FDT disintegration time test is shown in Table 3 with FDT (F3) having the fastest disintegration time, due to the higher levels of CCS used in F3 than F1 and F2. The results of the statistical test of tablet disintegration time have a sig value ($p<0.05$) means that each formula is significantly different. CCS has a dual mechanism, namely water wicking and rapid swelling [8]. The highly porous form of the structure speeds up the disintegration time, because water quickly enters the tablet and increases the tablet wetting rate, through the gaps between the granules and the granule pores [31]. This is related to the factor of the number of CCS super disintegrant excipient used in each formula intra and extra-granular. The use of intra and extra-granular affects the decrease in tablet disintegration time through the swelling mechanism, and along with the increase in the extra-granular CCS concentration, the disintegration time will be faster. The FDT disintegration pattern is also facilitated by intra-granular CCS which causes the tablets to be finely crushed not in the form of granules but into small particles so that the speed of disintegration is optimal. The optimum formula for FDT of bay leaf extract is shown in Table 4 with the results of all evaluations of the physical properties of the granules and FDT (F3) that meet the requirements and show the optimum results of physical parameters.

The results of this study are in line with the research of Puri *et al*. [24], that the combination of intra-granular and extra-granular can produce tablets with the most effective disintegration time by providing better tablet physical properties, compared to intra-granular or extra-granular only. Extra-crushing material granules have a high tendency to absorb water from the surrounding liquid through the tablet-breaking mechanism [32].

Tablets with disintegrant intra-granular have a higher hardness than tablets with extra granular crushing agents. By combining intra and extra granular super disintegrants, a good level of tablet hardness can be obtained so that the tablet is not brittle and has a faster disintegration time with the mechanism of tablet disintegration into granules (extra granular factor) and granules into small particles (intra granular factor).

Table 4. Various parameters of optimized tablet formula (F3)

No.	Test parameters	Optimized formula value
1.	Weight uniformity±SD (mg)	504.43±1.06
2.	Diameter±SD (mm)	12.00±0.00
3.	Thickness±SD (mm)	3.68±0.01
4.	Violence±SD (kg)	5.24±0.32
5.	Fragility±SD (%)	0.52±0.04
6.	Wetting time±SD (seconds)	20.00 ±2.65
7.	Disintegration time±SD (seconds)	19.67±3.06

4. CONCLUSION

In the FDT research, to improve the poor flow properties of the extract, the wet granulation method was carried out. The IPC results for the three formulas showed granules that met the requirements. This research provides information that the use of extra granular CCS at higher levels will increase the rate of disintegration. The combination of CCS intra granular 10 mg (2%) and extra granular 25 mg (5%) can produce FDT with the most effective. By combining intra and extra granular super disintegrants, a good level of tablet hardness can be obtained so that the tablet is not brittle and has a faster disintegration time. In addition, FDT bay leaves extract can be used as an alternative treatment for hyperlipidemia in patients who experience dysphagia. This research still needs development to determine the stability of FDT bay leaves extract where the active substance is herbal medicine.

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