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Research Article

Formulation and Evaluation of Fast Disintegrating Tablets Containing Broccoli Extract (*Brassica oleracea*) Using Crospovidone and Ac-Di Sol as Superdisintegrants

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ABSTRACT

Broccoli (*Brassica oleracea*) is known to contain flavonoid and glucosinolate compounds that act as acetylcholine enzyme inhibitors to improve memory in humans. To be practical and easy to use, broccoli is made in tablet dosage form. This study aims to determine the effect of the super disintegrants concentration of crospovidone and Ac-Di Sol on the physical quality of the Fast-Disintegrating Tablet (FDT) of broccoli extract. A total of 3 formulas were made using the wet granulation method and different concentrations of crospovidone and Ac-Di Sol, namely formula 1 (crospovidone 5% : Ac-Di-Sol 2%), formula 2 (crospovidone 4.5% : Ac-Di-Sol 2.5%), and formula 3 (crospovidone 4% : Ac-Di-Sol 3%). Tablet quality testing included hardness, friability, disintegration time, wetting time, and determination of total flavonoid content of tablet. The results of tablets have a brownish white colour with black spots, are round with a flat surface, have a distinctive odour, and have a slightly bittersweet taste. ANOVA statistical analysis of tablet hardness ($p > 0.05$) showed that there was no significant effect of crospovidone and Ac-Di-Sol concentrations on tablet hardness. While other test results showed a significant effect of crospovidone and Ac-Di-Sol concentrations on tablet friability ($p < 0.05$), disintegration time ($p < 0.05$), and wetting time ($p < 0.05$). Formula 1 (crospovidone 5% and Ac-Di-Sol 2%) is the best formula based on the physical quality of tablets, with an average tablet hardness value of 2.23 kp, friability of 0.95%, disintegration time of 1 minute 37 seconds, wetting time of 1 minute 15 seconds, and total flavonoid content of 2.62 mg QE/g (101.83%).

Keywords: Ac-Di-Sol; broccoli extract; crospovidone; fast disintegrating tablets; super disintegrants

INTRODUCTION

Broccoli (*Brassica oleracea*) is known to contain various beneficial compounds. Broccoli contains glucosinolates, phenolic compounds, fiber, and antioxidant compounds such as vitamins C, E, and A, carotenoids and polyphenols especially flavonoids and minerals (Ca, Mg, Se, and K) (Kusuma et al., 2017). Glucosinolates in broccoli can improve memory by inhibiting the acetylcholine enzyme (Yulia, 2007). The dose of broccoli extract has been shown to enhance memory in male mice with a dose of 0.069 g/kg/BW, when converted to a human dose, the dose becomes 0.19 g/50kg human BW (Nihaya, 2016).

Dementia is a syndrome that reduces intellectual ability and cognitive function, such as social skills, work, and daily activities, and occurs in elderly patients (Smeltzer & Bare, 2001). Drinking of water plays an important role in assisting the swallowing of oral medicinal preparations. However, many people, especially elderly patients, often have difficulty swallowing conventional preparations when water is not available, such as during motion sickness

(kinetosis) or during a sudden cough due to flu, allergies or bronchitis. To overcome these problems, rapid disintegrating tablets have emerged as a new preparation that is gaining popularity. Rapid disintegrating tablet can be accepted as a new drug delivery system that aims to provide drug safety because it is easy to administer, resulting in better patient compliance. The alternative dosage form that is more practical and attractive is developed as Fast Disintegrating Tablet (FDT) tablets which disintegrates instantaneously in togue, leading to release of drug when dissolve or disperses into saliva. The faster the drug dissolves, the faster it is absorbed and produces clinical effects. FDTs are designed to disintegrate quickly in the mouth, usually in less than 60 seconds after contact with saliva (Putranti et al., 2021). FDT preparations can disintegrate in less than 3 minutes (BP, 2014).

Some drugs can be absorbed through the mouth, pharynx and esophagus as saliva carries the drug to the stomach. This makes the bioavailability of the drug much higher compared to the conventional tablet form. The advantage of fast dissolving dosage forms is increasing in both, industry as well as academics (Nurdianti et al., 2018). The main approach in development of FDT is to use of superdisintegrants which are expected to have faster disintegration power (Ariestiawati et al., 2017). The superdisintegrants used in this study was a combination of crospovidone and Ac-Di Sol because it has a working mechanism that can absorb water (wicking) quickly and cause the tablet to expand quickly (swelling) so that it will accelerate the tablet breaking process. These two mechanisms are not owned by other super disintegrants that only rely on swelling (Putranti et al., 2021). Several studies have shown that the combination of crospovidone and Ac-Di Sol is more effective in accelerating disintegration time than the use of a single super disintegrant.

METHODS

Tools and Materials

The tools used include glassware (Pyrex®), analytical balance (Lab Pro®), juicers (Philips®), ovens (Memmert®), furnaces (Ney®), moisture balances (Optika®), vacuum dryers (Ogawa®), tablet presses (Labtron®), UV-Visible spectrophotometer (Jasco V-730®), calipers (Tricle brand®), tap density testers (TDT-1H®), hardness testers (YD-II®), friability testers (CS-2®), flowability testers (Intralab Trading Mandiri®). The materials used include broccoli, aluminum chloride ($AlCl_3$), aspartame, distilled water, crospovidone (Kollidon CL-F®, BASF), Ac-Di Sol (Crosscarmellose sodium®, PT IMCD Indonesia), robusta coffee essence (Subur Kimia Jaya, Jakarta, Indonesia), standard quercetin 98 % (Sigma aldrich, USA), magnesium stearate (Asian, Semarang, Indonesia), mannitol (Asian, Semarang, Indonesia), ethanol 70 % and methanol (Brataco, Bogor, Indonesia), sodium acetate, PVP K-30, and talc (Asian, Semarang, Indonesia).

Preparation and Evaluation of Broccoli Dry Extract

Broccoli was extracted using a juicer (Philips®) without additional water (filtrate 1). The dregs were added with water (1:1.5), and then juiced again (filtrate 2). Filtrates 1 and 2 were mixed, then filtered and dried with a vacuum dryer (Ogawa®) at a temperature of 50 oC for 4 hours. The quality of extract was test by determined the organoleptic (observation of color, odor, taste, and shape), determination of water content using the gravimetric method using an oven (Memmert®), with the requirement <10%, and determination of ash content using a furnace (Ney®), with the requirement <16.6% (DepKes RI, 2008).

Determination of Total Flavonoid Content of Broccoli Extract

Determination of total flavonoid content using quercetin analysis markers using a UV-Visible Spectrophotometer (Jasco V-730®). The standard quercetin solution was made with a concentration of 100 ppm then added methanol, 10% $AlCl_3$, 1 M sodium acetate, and distilled water, then the absorbance was measured using a UV-Visible Spectrophotometer at a wavelength of 400-450 nm (Chang et al., 2002). Determination of the optimum incubation time using a 100 ppm quercetin standard solution with absorbance measurements at 5, 10, 15, 20, 25, and 30 minutes, until a stable optimum incubation time was obtained (Chang et al., 2002). Quercetin standard curve was prepared with quercetin standard solution in concentrations of 2, 4, 6, 8, 10,12, and 14 ppm. Concentration and absorbance data were used to create a calibration curve with the linear regression equation $y = bx + a$ (Chang et al., 2002). Determination of total flavonoid content of broccoli extract by weighing 190 mg of extract then dissolving with methanol, adding 10% $AlCl_3$, 1 M sodium acetate, and distilled water. The solution was shaken until homogeneous then

incubated at optimum time, then the absorbance was measured at maximum wavelength.

Preparation and Evaluation of Tablet

Formula and Preparation

FDT containing broccoli extract was made in 3 formulas with different combinations of superdisintegrants ingredients. The formula consisted of 47.5 mg (23.75%) of active ingredients of broccoli dry extract with different combinations of superdisintegrants, namely (F1 Crospovidone 5%: Ac-Di-Sol 2%), (F2 Crospovidone 4.5%: Ac-Di-Sol 2.5%) and (F3 Crospovidone 4%: Ac-Di-Sol 3%). Each formula was made in 500 tablets with a weight per tablet of 200 mg. The formula is in Table 1.

FDT containing broccoli extract preparation was made using the wet granulation method. Each ingredient was sieved with a 30-mesh sieve and then weighed according to the formula. The initial stage was the preparation of a PVP K-30 binder solution in 70% ethanol. Furthermore, the inner phase was mixed consisting of dry broccoli extract, crospovidone, Ac-Di Sol, and aspartame, then the binder solution and robusta coffee essence were added. The mass was mixed until homogeneous and moist and then sieved using an 8-mesh sieve. The wet granules were dried in an oven (Memmert®), at a temperature of 60 ºC. The dried granules were sieved again with a 16 mesh sieve and then the outer phase, namely magnesium stearate and talc, was added.

Furthermore, the quality of the obtained granules was tested including: Determining the water content of the granules using a moisture balance (Optika®), with the condition that the water content is generally not more than 2-5% (Manno & Setianto, 2022). Flow rate test using a flowability tester (Intralab Trading Mandiri®) by measuring the time the granules flow (Nurdianti et al., 2018). The angle of repose test by flowing the granules through a funnel and collecting at the bottom. The formed mounds are measured for their height and radius (Lachman & Kanig, 2008). Determination of the Compressibility Index and Hausner Ratio, using a tap density tester (TDT-1H®),and recording the initial volume and final volume after tapping 300 times (KemensKes RI, 2014). The granules that have met the requirements are then compressed using tablets machine (Labtron®), and tested for quality.

Evaluation of Tablets

Organoleptic testing of tablets carried out visually including testing the physical condition of the tablet such as color, odor, taste, and shape as well as other physical conditions of the tablet. Weight variation, ten tablets were taken, weighed with digital scales (Lab Pro®) and calculated the average weight. Tablet weight uniformity, calculated the amount of active substance in each tablet based on the results of determining the level of each tablet, then calculated the acceptance value. The requirement for tablet weight uniformity is 98.5% ≤ $\bar{X}$ ≤101.5% (KemenKes RI, 2014).

Tablet thickness was measured using a caliper (Tricle brand®). Twenty tablets from each formula were used and the average value was calculated. The requirements for tablet size uniformity are the diameter of the tablet no more than 3 times and no less than 1 1/3 of the tablet thickness (KemenKes RI, 2014). Tablet hardness was measured using a Hardness Tester (YD-II®), Twenty tablets of each formula were tested and the average reading was recorded. A good FDT hardness is 1-3 kg/cm2 (Prajapati & Ratnakar, 2009).

Friability test, 40 tablets were weighed and inserted into the Friabilator (CS-2®), then the device was rotated at 25 rpm for 4 minutes. The tablets were removed, cleaned and weighed again. The percentage of tablet friability was calculated. The requirement for tablet friability is no more than 1% (USP, 2020). Disintegration time, based on the procedure (BP, 2014) by placing the FDT in a 5 cm diameter petri dish filled with 20 mL of water. The disintegration time required by 6 tablets is recorded and then the average is calculated with the condition that it is not more than 3 minutes (BP, 2014).

Wetting Time test, a Petri dish containing 6 mL of distilled water was prepared. Inserted tablets containing a small amount of red dye were placed on it. The time required for the top surface of the tablet to become completely red was recorded (Putranti et.al., 2021). Drug Content Uniformity, Twenty tablets were powdered in mortar and the blend equivalent to 190 mg of broccoli dry extract was weighed and dissolved in methanol and stirred with a magnetic stirrer for 10 minutes. The filtrate obtained was put into a measuring flask, then added 10% $AlCl_3$, 1 M sodium acetate, and distilled water to the boundary mark. The solution was homogenized, then incubated at the optimum time and the absorbance was measured at the maximum wavelength (Rahmahuda, 2016).

Table 1. Formula FDT Broccoli Extract

Ingredients	Function	Formula numbers / content (%w/w)		
		1	2	3
Broccoli Dry Extract	Active substance	23.75	23.75	23.75
Crospovidone	Superdisintegrant	5	4.5	4
Ac-Di Sol	Superdisintegrant	2	2.5	3
PVP K-30	Blinder	2.5	2.5	2.5
Magnesium stearate	Lubricant	0.5	0.5	0.5
Talc	Glidant	1	1	1
Aspartame	Sweetener	4	4	4
Essence coffee	Flavor	2	2	2
Mannitol ad	Filler	100	100	100

Data Analysis

The results of the tablet physical properties test, such as hardness, friability, disintegration time, and wetting time, were compared with the theoretical standards listed in the Indonesian Pharmacopoeia and other references related to Fast Disintegrating Tablet (FDT) criteria. The data were then analyzed using SPSS test (one-way ANOVA) and continued with Duncan's further test.

RESULTS AND DISCUSSION

Evaluation of The Broccoli Dry Extract

Broccoli dry extract was made by the extraction method using a juicer extraction because it does not take a long time, has high purity, and can maintain the content of active compounds in the fruit or vegetables (Lee et al., 2017). The use of a juicer produces broccoli juice with a higher flavonoid content compared to broccoli juice extracted with a smoothie tool and hand blender (Lee et al., 2017). The yield of broccoli dry extract obtained was 3.02%. Broccoli dry extract has a slightly coarse powder form, brownish-green color, bitter taste, and a strong distinctive aroma (Figure 1). The average water content of broccoli dry extract was 5.6924% ± 0.7367, meeting the requirements of <10%, while the average ash content of broccoli dry extract was 3.5455% ± 0.1525, meeting the requirements of <16.6% (Depkes RI, 2008).

Figure 1. Broccoli dry extract.

Total Flavonoid Content of Broccoli Dry Extract

The determination of total flavonoid content of broccoli dry extract was carried out using the calorimetry method using a Visible spectrophotometer with quercetin analysis markers, as well as $AlCl_3$ and sodium acetate reagents. The results of the maximum wavelength measurement obtained were 434.5 nm with an optimum incubation time of 25 minutes. The regression equation obtained was y = 0.0668x + 0.0014 with a correlation coefficient (R2) = 0.9978. Based on the linear regression calculation, the average total flavonoid content of broccoli extract was 2.57 mg QE/g ± 0.0942. These results are different from previous research (Hidayat, 2024) with a total flavonoid content of broccoli extract obtained of 4.88 mg QE/g ± 0.09. This difference can be caused by different planting locations, drying temperatures, and drying times of the extract.

Table 2. Evaluation Parameters of Broccoli Extract Granule

Formula number (*Crospovidone* : Ac-Di Sol)	Water Content (% w/w ± SD)	Flow Rate (g/s ± SD)	Angle of Repose (º± SD)	Compressibility Index (% ± SD)	Hausner ratio (± SD)
1 (5% : 2%)	3.76 ± 0.18	4.33 ± 0.29	28.09 ± 0.89	7.81 ± 0.91	1.08 ± 0.01
2 (4.5% : 2.5%)	3.35 ± 0.18	4.41 ± 0.42	27.06 ± 1.01	11.93 ± 0.12	1.13 ± 0.00
3 (4% : 3%)	3.18 ± 0.06	4.91 ± 0.87	25.19 ± 0.81	12.30 ± 0.88	1.14 ± 0.01

Note: Data are given as mean±SD, n=3

Evaluation of Granule

Evaluation of granule quality is carried out to assess the quality of granules before going through the molding process into tablets. Evaluation of granule quality includes testing of water content, flow rate, angle of repose, compressibility index, and Hausner ratio. The results of the granule quality evaluation are presented in Table 2.

The results of the granule quality evaluation showed that the three formulas had a water content that met the requirements, namely 2-5% (Lachman, 2008). The purpose of the water content test was to determine the amount or percentage of water contained in the granules after the drying process. The results of the granule flow rate test of the three formulas were in the range of 4-10 g/s, included in the good flow rate properties (Aulton, 2002). The size and shape of the granules affect the flow rate, the larger the granule size, the better the flow (Sya'bania et al., 2021). The results of the angle of repose test of the three formulas were in the range of 25-30o, included in the very good category (USP, 2020). The faster the flow time, the smaller the resulting angle of repose, and conversely the slower the flow time, the larger the resulting angle of repose (Puspita et al., 2022). The compressibility index and Hausner ratio test data of the three formulas showed that F1 had the best results compared to F2 and F3 (USP, 2020). This is because the concentration of crospovidone superdisintegrants used was the highest in F1. Crospovidone has better compactibility and compressibility than superdisintegrants Ac-Di Sol because of its porous and hollow structure, so it will be able to increase the humidity of the granules to strengthen the bonds between particles in the granules (Farahiyah & Sulaiman, 2021). Granules that have good compressibility and Hausner ratio values will facilitate the tablet printing process to produce compact tablets (Anggraeni et al., 2023).

Evaluation of Tablets

The results of the tablet evaluation were carried out to determine the physical quality of the tablets including organoleptic testing, weight uniformity, size uniformity, hardness, brittleness, disintegration time, and wetting time. The results of the organoleptic test of the three broccoli extract FDT formulas obtained a round shape with a flat surface, brownish white with black spots, a sweet and slightly bitter taste, and a strong distinctive broccoli odor. The broccoli extract FDT can be seen in Figure 2.

Figure 2. FDT of Broccoli Extract.

The results of weight uniformity showed that the three formulas meet the requirements for weight uniformity with a content of 98.5-101.5% (KemenKes RI, 2014). The acceptance value (NP) of the three formulas meets the requirements with an acceptance value of <15% (KemenKes RI, 2014). While other quality results are in Table 3.

Table 3. Evaluation Parameters of Broccoli Extract FDT

Evaluation Parameters	F1	F2	F3
Size Uniformity			
- Thickness (cm) ± SD	0.4015 ± 0.0028	0.3902 ± 0.0083	0.3865 ± 0.0089
- Diameter (cm) ± SD	0.8115 ± 0.0023	0.8115 ± 0.0023	0.8110 ± 0.0020
*Hardness (kg/cm^2) ± SD	2.23^{a} ± 0.48	2.25^{a} ± 0.54	2.28^{a} ± 0.67
*Friability (%) ± SD	0.9510^{a} ± 0.0494	0.9406^{b} ± 0.0414	0.6492^{b} ± 0.1499
*Disintegration time (min'sec") ± SD	$01'37"^{a}$ ± 0.42	$03'21"^{b}$ ± 0.23	$04'16"^{c}$ ± 0.20
*Wetting time (min'sec") ± SD	$01'15"^{a}$ ± 0.29	$02'59"^{b}$ ± 0.39	$03'39"^{c}$ ± 0.12

Note: Data are given as mean±SD, n=3

* Numbers followed by different lowercase letters indicate a significant difference ($p<0.05$)

The results of the uniformity test of the size of the three formulas met the requirements with a tablet diameter of not less than 1 1/3 of the tablet thickness and not more than 3 times the tablet thickness (Nofriyaldi et al., 2019). The hardness values of the three FDT formulas met the requirements in the range of 1-3 kg (Prajapati & Ratnakar, 2009). Formula 3 produced the highest hardness because the use of Ac-Di Sol concentration in the formula has the largest amount. After all, it functions as a strong binder so that it produces tablets with high hardness (Sholikhah, 2017). Ac-Di Sol in addition to being used as a disintegrant can also function as a binder (Sya'bania et al., 2021). The tablet friability value shows that the three formulas meet the requirements, namely <1% (USP, 2020). The lowest and best friability value is in Formula 3. This is because the use of crospovidone concentration as a super disintegrant in small amounts will reduce the brittleness of the tablet.

The relationship between brittleness and tablet hardness is inverse, the higher the hardness of the tablet, the lower the brittleness value (Bestari, 2020). According to the requirements, the FDT disintegration time is no more than 3 minutes (BP, 2014). The results of the disintegration time test showed that only F1 met the requirements, compared to other formulas. This can be caused by the concentration of Ac-Di-Sol used in F2 and F3 being more than F1. The higher concentration of Ac-Di-Sol can increase the formation of gel on the tablet when in contact with water which causes the tablet not to disintegrate easily which will inhibit the tablet disintegration time (Sholikhah, 2017). Based on the results of the FDT wetting time test, F1 has the fastest wetting time compared to F2 and F3. Although there are no special requirements for FDT wetting time, a faster wetting time is considered better because it will accelerate the tablet disintegration time (KemenKes RI, 2020). F3 with a large amount of Ac-Di Sol can reduce the porosity of the tablet so that water absorption is used first to expand to the side before wetting the top of the tablet (Sholikhah, 2017).

All data were statistically analyzed using ANOVA, for analysis of tablet hardness value obtained ($p > 0.05$) indicating that there was no significant effect of crospovidone and Ac-Di-Sol concentration on tablet hardness. The hardness of the three formulas was almost similar. Analysis of tablet friability value obtained ($p < 0.05$) indicating a significant effect of crospovidone and Ac-Di-Sol super disintegrant concentration. Duncan's further test results showed that F2 and F3 had lower and better brittleness and were significantly different from F1. Analysis of tablet disintegration time value obtained ($p < 0.05$) indicating a significant effect of crospovidone and Ac-Di-Sol concentration. Duncan's further test results showed a significant effect on tablet disintegration time in each formula. The fastest disintegration time and meeting the requirements was in Formula 1. Analysis of the tablet wetting time test obtained ($p < 0.05$) showed a significant effect of the concentration of crospovidone and Ac-Di-Sol. The results of Duncan's further test showed a significant effect on the tablet wetting time of each formula with the fastest time in Formula 1.

Results of Determination of Total Flavonoid Content of Fast Disintegrating Tablet (FDT)

Determination of total flavonoid content of FDT was carried out to determine the level of quercetin flavonoids contained in the tablet. Measurements were carried out quantitatively using UV-Visible spectrophotometer with the colorimetric method (Table 4).

In general, the active substance content in tablet preparations is 90-110% (KemenKes RI, 2020). Based on the results obtained, the three formulas meet these requirements. There was a decrease in the total flavonoid content of FDT between formulas. The decrease in content can be influenced by the use of super disintegrant Ac-Di-Sol, which functions as a disintegrant and a binder (Sya'bania et al., 2021). So it is suspected that when the analysis of quercetin flavonoid content was carried out, the extract was still strongly bound to the additional ingredient Ac-Di-Sol. Based on the results of the ANOVA test on the total flavonoid content of FDT, the value obtained ($p < 0.05$) showed that there was a significant effect of the concentration of super disintegrant Ac-Di-Sol on the total flavonoid content of FDT. The results of Duncan's further test on the total flavonoid content of FDT showed that there was a significant difference in the total flavonoid content of FDT in all formulas. Formula 1 provided the highest flavonoid content. It can be seen that the lower the concentration of Ac-Di Sol, the higher the total flavonoid content in FDT.

Table 4. Content of Total Flavonoid for Broccoli Extract FDT

Formula Number (*Crospovidone* : Ac-Di-Sol)	*Content of Total Flavonoid (mg QE/g) ± SD	Content of Total Flavonoid (%)
1 (5% : 2%)	2.6181[a] ± 0.0016	101.83
2 (4.5% : 2.5%)	2.6093[b] ± 0.0016	101.48
3 (4% : 3%)	2.4659[c] ± 0.0002	95.91

* Numbers followed by different lowercase letters indicate a significant difference ($p<0.05$)

CONCLUSION

Fast Disintegrating Tablet (FDT) of broccoli extract that has the best quality is Formula 1 with a superdisintegrants concentration of crospovidone 5% and Ac-Di Sol 2%.

CONFLICT OF INTEREST

There was no conflict of interest in this manuscript.

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