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Research Article

Orally Disintegrating Tablet Formulation of Avicennia Fruit Ethanol Extract (*Avicennia marina*)

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Abstract: The fruit produced from Avicennia tree (in the form of ethanol extract) has the property of reducing blood glucose levels (oral antidiabetic mellitus) with an effective dose of 10 mg / 50 kg human body weight. Most of the elderly with diabetes mellitus in Indonesia are aged 60-74 years (83.3%) who have a decreased ability to swallow drugs. In addition, antidiabetic drugs are expected to be able to produce fast action, so that it can reduce blood sugar levels immediately. Therefore, the Avicennia fruit ethanol extract formulated in the form of Orally Disintegrating Tablet (ODT). The aim of this study was to determine the effect of Starch 1500 and Crospovidone as a superdisintegrant in either single or combination use in the Avicennia fruit ethanol extract ODT formulation. The ODT was made by direct compression. There were three formulas that was carried out in this study : FI with 10 mg of Starch 1500, FII with 10 mg of Crospovidone and FIII with a combination of superdisintegrant Starch 1500 and Crospovidone (7 mg and 3 mg). In this study it could be conclued that the best compatible superdisintegrant in ODT for Avicennia fruit ethanol extract was Crospovidone, not combination with Starch 1500.

Keywords: Avicennia. Crospovidone, Starch, Orally, Disintegrating Tablet, Antidiabetic_mellitus

1. INTRODUCTION

Avicennia marina is a mangrove tree species that is most often found on the coast of tropical countries, including Indonesia [1]. Avicennia tree has fruit which in Indonesia is known as "Api-Api" fruit. Avicennia fruit is empirically used for traditional medicine. A study from Setiawati, et al. (2016) showed that the ethanolic extract of Avicennia fruit could have antidiabetic effect [2]. This is thought to be due to the flavonoid content of the etanol extract of the Avicennia fruit. Flavonoids have been shown to have beneficial effects on diabetes mellitus, both through their ability to reduce glucose absorption and by increasing glucose tolerance [3]. The effective dose of Avicennia fruit ethanol extract as antidiabetic mellitus obtained based on this study was 10 mg/50 kg body weight for humans.

Most of the elderly with diabetes mellitus in Indonesia are aged 60-74 years (83.3%) who have a decreased ability to swallow drugs. In addition, antidiabetic drugs are expected to be able to produce fast action, so that it can reduce blood sugar levels immediately. An antidiabetic drugs are expected to be able to produce fast action, so that they can immediately lower blood sugar levels. Therefore, a tablet formulation that is capable of disintegrating rapidly is needed. One alternative dosage form is Orally Disintegrating Tablet (ODT) or often called Fast Disintegrating Tablet (FDT), which is one of the technological innovations in the field of formulation technology.

The use of antidiabetic drugs in the form of ODT is expected to make it easier for elderly diabetic patients who have difficulty swallowing drugs. In addition, ODT can be used in children who cannot swallow tablets, as well as people who experience nausea. This will facilitate and improve patient compliance in using the drug [4].

Disintegrant is an important additive to accelerate the disintegration time of ODT. There are now a large number of materials known as disintegrants that are created by modifying natural polymers or by chemical synthesis [5]. Superdisintegrants are a new generation of disintegrant novel type. When they come into touch with water, they cause compact breakdown in a matter of minutes. The most widely used superdisintegrants include starch 1500 and crospovidone [6]. They raise the hydrostatic pressure via swell or wicking water, or by a combination of both methods [7]. Both crospovidone and starch have physicochemical characteristics including different hygroscopic levels, which can affect the dissolution time of ODT preparations.

Based on these considerations, a research was carried out on the manufacture of ODT containing ethanol extract of Avicennia fruit as antidiabetic mellitus that meets the requirements of pharmaceutical preparations using superdisintegrant starch 1500, crospovidone and their combination which provide disintegration time and physical characteristics of the tablet.

2. MATERIALS AND METHODS

The object of this research was the physical characteristics of a mixture of powders and tablets from ODT containing Avicennia fruit ethanol extract using the superdisintegrant Starch 1500, Crospovidone and their combination.

The independent variables in this study were superdisintegrants, namely Starch 1500 (10 mg), Crospovidone (10 mg), and combination of Starch 1500 and Crospovidone (7 mg and 3 mg) in Orally Disintegrating Tablet (ODT) containing Avicennia fruit ethanol extract.

The dependent variable in this study was the physical characteristics of the powder mixture including moisture content and flow time; tablet physical characteristics which include weight uniformity, hardness, friability, wetting time and disintegration time. The controlled variables in this study were the tablet formula, the method and process of manufacturing tablets, the method of testing the mixture of mass print and tablets of Orally Disintegrating Tablet (ODT) containing Avicennia fruit ethanol extract, as well as the materials and tools used.

The ingredients for the manufacture of Avicennia fruit ethanol extract were Avicennia fruit and 96% ethanol. The ingredients for the tablet formula were Avicennia fruit ethanol extract, mannitol, avicel PH 102, starch 1500, crospovidone, Mg-stearate, talcum, aspartame and apple flavor.

The tools used were for the process of making Avicennia fruit extract: a drying cabinet, a large dark bottle closed for maceration and an evaporator. Tools for the tablet manufacturing process : ordinary scales, analytical balances, single punch tablet machine. Tools for evaluating mixtures of powders and tablets: humidity tester and mass powder flow time instrument, tablet hardness tester, friability tester, disintegrant tester, analytical balance, and petri dish.

2.1. Preparation of Avicennia Fruit Ethanol Extract

The fruit of Avicennia was cleaned of impurities by using clean water. The cleaned fruit was then dried in a drying cabinet at 50ºC until dry. The dried simplicia was then blended and sifted. Avicennia fruit powder was macerated with 1 liter of 96% ethanol for 5 days, until the filtrate was clear. The filtrate from this filtration was combined and evaporated with a rotary evaporator until a

thick extract was obtained. Furthermore, the viscous extract obtained was subjected to phytochemical screening tests including preliminary and confirmatory tests for secondary metabolites of flavonoids. alkaloids, tannins, saponins and steroids.

2.2. Formulation and making ODT containing Avicennia Fruit Ethanol Extract

ODT preparation of Avicennia fruit ethanol extract was carried out by direct compression /method. All ingredients in each formula (Table 1), except Mg stearate and talcum were mixed until homogeneous. After the mass was homogeneous, it was then mixed with Mg stearate and talcum for 5 minutes. Tablet mass testing included humidity and flowability. The homogeneous mass was then tableted with a Maksindo TBL-55 single punch tablet machine. Tablets were printed with an average weight of 100 mg.

Table 1. Formulation of ODT Containing Avicennia Fruit Ethanol Extract

Material (mg)	**FI**	**FII**	**FIII**
Avicennia fruit ethanol extract	10	10	10
Starch 1500	10	0	7
Crospovidone	0	10	3
Aspartam	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5
Talk	1	1	1
Apple flavor	qs	qs	qs
Avicel PH 102	30	30	30
Mannitol	Ad 100%	Ad 100%	Ad 100%

2.2.1. ODT Print Mass Testing

Tablet mass testing included humidity and flowability. The procedure of determining these tests was based on Aulton method [8]. Loss of drying was analyzed using a drying shrinkage measuring tool, Moisture determination balance (Ohaus).

Flowability was determined as follows, the tablet mass was put in the funnel of a flow rate test tank with the bottom closed (Granulate tester GT/GTB Erweka) to assess flowability. The time necessary for the amount of powder to drop down the test tool funnel was determined in the flow velocity by utilizing the stopwatch from the commencement of the bottom cap opening until all of the granular mass flows out of the test apparatus.

2.2.2. ODT Quality Testing

Tablet quality testing includes weight uniformity, hardness, friability, wetting time, disintegration time. Weight uniformity test was based on Indonesian Pharmacopeia III [9]. Hardness was determined using Hardness tester (Hardness Mitotuyo Japan). Friability was assessed using a friability tester (Friability tester TA-10/TA-20) that weighted tablets by about twenty tablet before being put into tablet friability testers. The tool runs at twenty-five lap speeds per minute for four minutes. Tablets were still intact weighed, then calculated to lose weight. The maximum weight reduction allowed was 0.8 percent, according to USP XXVII [10].

3. RESULTS AND DISCUSSION

Direct compression method was used in this study to produce ODT containing Avicennia Fruit Ethanol Extract, because the method of direct compression provides a disintegrating faster than with

the wet granulation method. Avicel PH 102 was used as filler-binder and combined with mannitol as a filler, so as to form the desired tablet size. Avicel PH 102 was chosen because it has a larger particle size than Avicel PH 101, so that the resulting flowability is better than Avicel PH 101 which has a smaller particle size. In addition, Avicel PH 102 is also widely used as a filler-binder in the manufacture of tablets using the direct compression method. A combination of Avicel PH 102 and mannitol was also made, with the aim of masking the bitter taste of the ethanol extract of avicennia.

As an anti-fractional agent within all the formula of this ODT was used talcum and magnesium stearate. The use of these two anti-fractional agent at the same time was meant to produce a decent lubricant impact on tablet formulas, which, both advantages differed from one another. Talcum with a degree of 1-5% might provide good anti-adherent and glidant effect however had poor lubricant effect, whereas magnesium stearate with concentration 0.25-5% could have good lubricant effect but had less anti-adherent and glidant effect good. It absolutely was hoped that by combining the two excipients might increase the mass flow of pill prints upon coming into the tablet mold, it could stop the projected of the print mass of tablets on punch and die and could build the dose additional glossy, therefore increasing the aesthetic worth of the tablet itself.

3.1. The Result of Mass Print of ODT containing Avicennia Fruit Ethanol Extract

Testing the print mass of the tablet was done before tableting. This test was expecting to decide whether or not the print mass was printed into tablets, so this test may well be utilized as a supporting figure to decide the quality of tablets to be printed. There were a few prerequisites that must be met for the printing mass of the tablet to be printed legitimately, counting moisture content and flowability. The physical characteristics test results of ODT print mass containing avicennia fruit ethanol extract were showed in Table 2.

Table 2. Result of Mass Testing Print ODT Containing Avicennia Fruit Ethanol Extract

Testing	FI	FII	FIII
Humidity (%)	2.15 ± 0.02	1.81 ± 0.02	0.95 ± 0.01
Flow time (seconds)	1.79 ± 0.52	2.32 ± 0.30	1.41 ± 0.17

FI : Starch 1500 10%, Crospovidone 0%

FII : Starch 1500 0%, Crospovidone 10%

FIII : Starch 1500 7%, Crospovidone 3%

Figure 1. Appearance of ODT Containing Avicennia Ethanol Extract : a) FI b) F II c) FIII

The results of the moisture test of the print mass mixture showed that the formula with superdisintegrant Starch 1500 was higher than the formula with Crospovidone and its combination. High humidity would make the powder mixture moist and causing the powder to not be free flowing

and would stick in die and punch of the tablet machine. Pregelatinized starches, such as Starch 1500 are polysaccharides containing glucose monomers in various forms linked by α-1.4 bonds. The glucose units in starch made it have a highly hydrophilic hydroxyl group. Pregelatinized starch (Starch1500) has a high LOD, but has the lowest water activity and therefore the highest ability to bind water molecule, including water molecules in air humidity [11]. This is linear with the results of the humidity test which shows that the formula with the highest Starch1500 has the highest humidity.

The flowability test result showed that in Formula II when Crosspovidone was higher, the flow time was also long. In the research of Sa'adah and Fudholi (2011) [12], the higher the specific gravity of a powder, the faster its flowability. It is known that Starch 1500 has a specific gravity of 0.88 g/mL and Crosspovidone has a specific gravity of 0.273 g/ml [13].

3.2. The Result of Quality Testing of ODT containing Avicennia Fruit Ethanol Extract

Table 3. Physical Characteristics Test Results of ODT Containing Avicennia Fruit Ethanol Extract

Testing	FI	FII	FIII	Positive Control
Weight uniformity (mg)	108.2 ± 1.62	101.4 ± 2.60	101.2 ± 1.42	151.9±0.69
Hardness (kg/cm^2)	1.7 ± 0.34	1.6 ± 0.37	1.9 ± 0,21	2.25±0.26
Friability (%)	0.21 ± 0.17	0.19 ± 0.22	0.13 ± 0.10	0.12±0.21
Wetting time (seconds)	22.33 ± 2.08	58.33 ±11.59	31.67 ± 5.03	5.18±0.48
Disintegration time (seconds)	152.67 ± 10.38	112 ± 15.52	124.67 ± 10.45	7.54±0.52

FI : Starch 1500 10%, Crospovidone 0%

FII : Starch 1500 0%, Crospovidone 10%

FIII : Starch 1500 7%, Crospovidone 3%

Positive Control : Ondavell® 8 mg ODT

The filling volume used in this tableting process was set to a weight of 100 mg by adjusting the bottom punch of the tableting machine. The Indonesian Pharmacopoeia III states that tablets weighing 26-150 mg should not contain more than two tablets that deviate by more than ten percent (90-110 mg) and no more than one tablet with a deviation of more than 20% (80mg-120mg). The results of this study as listed in table 3, all tablets produced met the specified requirements.

Friability test could be seen from table 3 showed that tablets with superdisintegrant Starch 1500 had a higher friability than Crospovidone. Starch 1500 and Crospovidone were both hygroscopic but the presence of high moisture content caused less strong bonding between the tablet constituent particles. Therefore the resulting tablet had a high friability. However, all formulas had met the requirements in accordance with USP XXVII [10], i. e allowable weight loss is up to 0.8%.

The tablet hardness test showed that Crospovidone was a hygroscopic superdisintegrant so that it easily absorbs moisture and caused the tablet to have a low hardness causing the tablet to disintegrate quickly. Starch 1500 is a brand of pregelatinized maize starch being recommended as a disintegrant at proportions of 5–10%. It is considered a hygroscopic material with high water content, loss on drying 15% [13]. This was what caused the moisture content in the ODT mass print before tableting in FI was the highest compared to other formulas. However, the disintegration time showed that the formula with the fastest disintegration time was the formula with the superdisintegrant crospovidone (FII), not combination starch and crospovidone. This was because Starch 1500 had a lower water sorption capacity than crospovidone. Starch 1500 has a maximum water sorption of about 32%, while crospovidone has a maximum water sorption of 60% [13]. Also seen from the value

of water activity, Starch 1500 has an a_w value of 0.32 [14], while crospovidone has an a_w value of 0.7384 [15].

Table 4 shows that the results of the one-way ANOVA statistical test of the response values of hardness, friability, wetting time and disintegration time of ODT between all groups (FI, FII, FIII and positive control). The statistical results in table 4 show that the values of weight uniformity and friability were not significantly different between groups FI, FII, FIII and positive control (this can be seen from the significance value > 0.05), but significantly different in the values of hardness, disintegration time and wetting time (significance value < 0.05). While the tablet wetting time test showed significantly different results between the FI, FII, FII and positive control groups, so it was continued with the Post Hoc test.

Table 4. Statistical Test Results of Physical Characteristics of ODT Containing Avicennia Fruit Ethanol Extract All Groups (FI, FII, FIII) and Ondavell® ODT as Positive Control

Physical Characteristic Test	Significance	Conclusion
Weight uniformity (mg)	0,942	not significant difference
Hardness (kg/cm^2)	0,001	significantly different
Friability (%)	0,488	not significant difference
Disintegration time (seconds)	0,000	significantly different
Wetting time (seconds)	0,000	significantly different

Ondavell® ODT was used as a positive control as a comparison of the resulting product with products already on the market. When compared with the positive control, Avicennia Fruit Ethanol Ectract ODT product was significantly different, especially in the hardness test, wetting time and disintegration time. The results of the Post Hoc test showed that the hardness and disintegration time between the FI, FII and FIII groups were not significantly different, but compared to the positive control group they were significantly different. In general, the higher hardness value in the tablet will affect lowering disintegration time. This can be seen in the disintegration time of FI with only Starch 1500 having the highest disintegrant value compared to single crospovidone and its combination with crospovidone. The degree of gelatinization can also affect the water absorption rate. Fully gelatinized starch may show slower water uptake, and it is known that the gelatinization degree of Starch 1500 was 87.7% and it was a high degree[16]. Avicennia Fruit Ethanol Extract ODT products were indeed slower to wet and disintegrate than Ondavell® ODT products. However, when compared to conventional Avicennia Fruit Ethanol Extract tablets from previous studies, the disintegration time of Avicenna ODT products was faster, it was known in previous studies that formulating Avicenna tablets produced a disintegration time of 6.61 minutes [17].

The results of the Post Hoc test for the wetting time test showed that there were differences not only in the Avicenna ODT tablet group with Ondavell® ODT alone, but in the FI and FII (p value : 0.000) groups as well as the FII and FIII (p value : 0.000). Avicenna ODT tablets had a significant difference in wetting time. In Table 5 showed that the tablet group with only Starch 1500 disintegrant had the fastest wetting time than the single crospovidone group or the group with Crospovidone combination. This was because pregelatinized starch itself has more functional groups (Picture 2) to bind to water [18] compared to crospovidone (Picture 3), so pregelatinazed starch was wetted faster but has a longer disintegration time, due to the water sorption of Starch 1500 was lower than Crospovidone. Crospovidone also has a wicking mechanism so that the disintegration time was

quicker. Wicking is the ability of the tablet to absorb water when placed into a liquid so that it will make the particle bonds loosen and causing it to break [19].

Table 5. Wetting Time of ODT Containing Avicennia Fruit Ethanol Extract

Number of Replication	Wetting time (second)			
	FI	FII	FIII	Control Positive
1	23	45	37	5.85
2	20	64	27	5.72
3	24	66	31	4.74
Average	22,33±2,08	58,33±11,09	31,67±5,03	5,43±0,61

FI : Starch 1500 10%, Crospovidone 0%

FII : Starch 1500 0%, Crospovidone 10%

FIII : Starch 1500 7%, Crospovidone 3%

Positive Control : Ondavell® 8 mg ODT

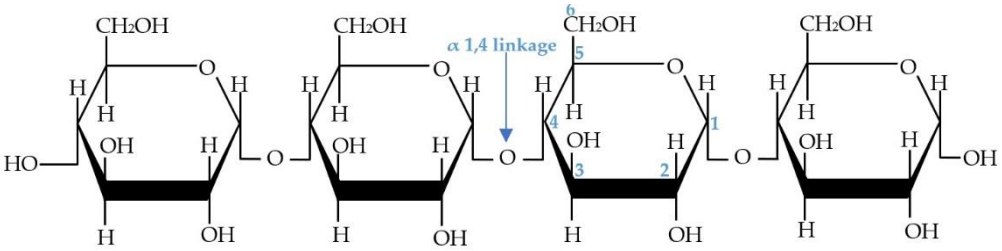

Figure 2. Segment of An Amylose Molecule of Pregelatinized Starch [18]

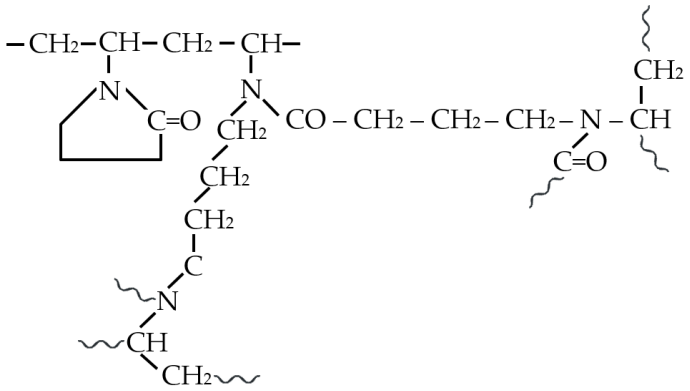

Figure 3. Crospovidone Structure [20]

Preparation of tablets specifically compressed tablet from the avicennia natural product extract has not however explored, but the inclination to create ODT from plant extricates that adequacy must be recognized has begun numerous within the intrigued of researcher. Lestari, et all (2018) formulated Fast Disintegrating Tablet (FDT) of *Centella asiatica* (L.) Urb. Ethanolic Extract and had used crosspovidone too as superdisintegrant [21]. Sa'adah, et.al (2019) formulated ODT of Tahongai Ethanol Extracts (*Kleinhovia hospita* L.) with Explotab as superdisintegrant [12].

4. CONCLUSION

The ethanol extract of Avicennia (*Avicennia marina*) fruit was successfully formulated into Orally Disintegrating Tablet (ODT) preparations by varying the super-disintegrant Starch 1500 and Crospovidone.

Orally Disintegrating Tablet (ODT) containing ethanol extract of Avicennia (*Avicennia marina*) fruit has good physical characteristics in terms of weight uniformity, hardness, friability, disintegration time and wetting time. The best compatible superdisintegrant for ODT containing Avicennia (*Avicennia marina*) ethanol extract was formula with with the superdisintegrant Crospovidone (FII) because it could produced the tablets disintegrate fastest.

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Conflicts of interest
The authors declare no conflict of interest.

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