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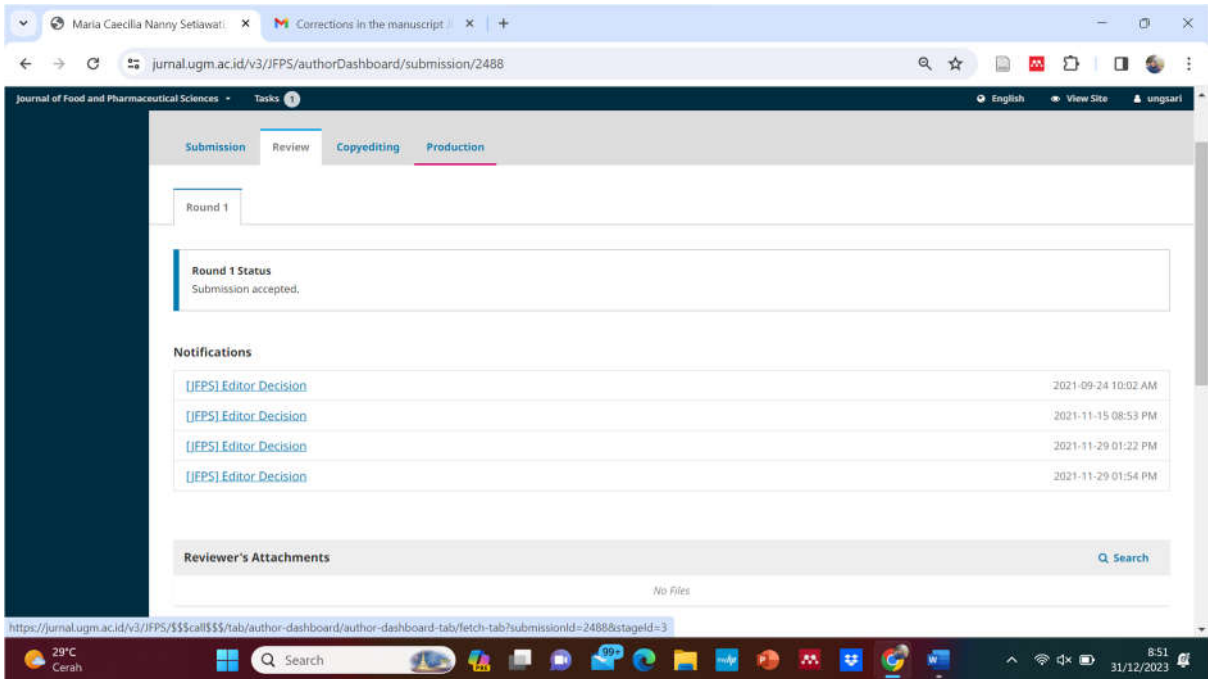
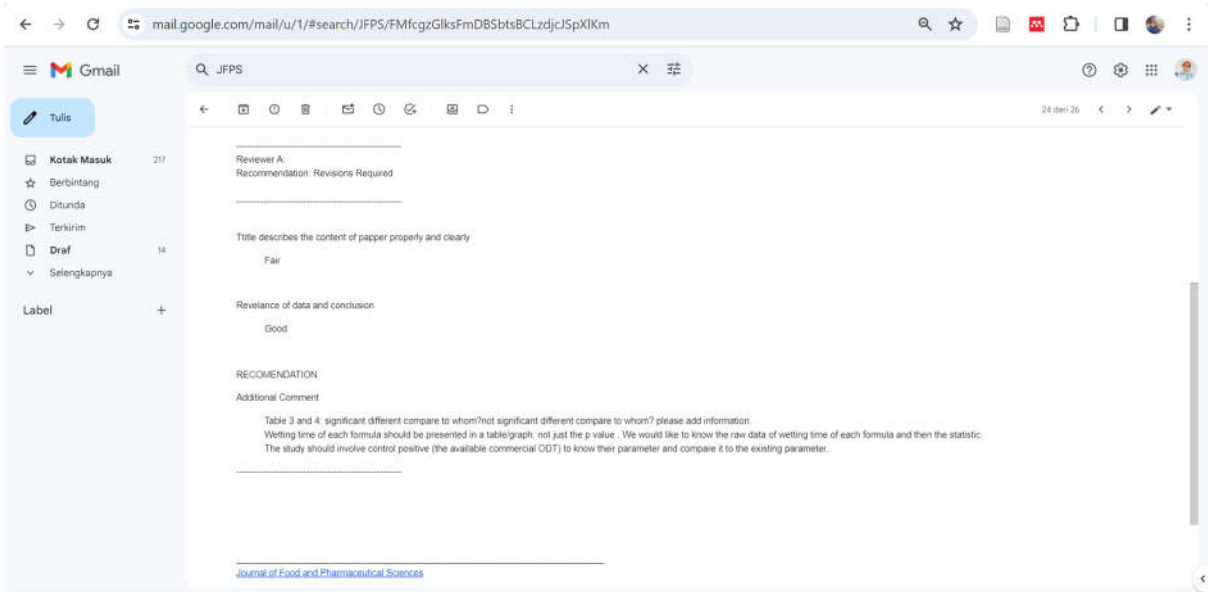
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desmayanti@gmail.com

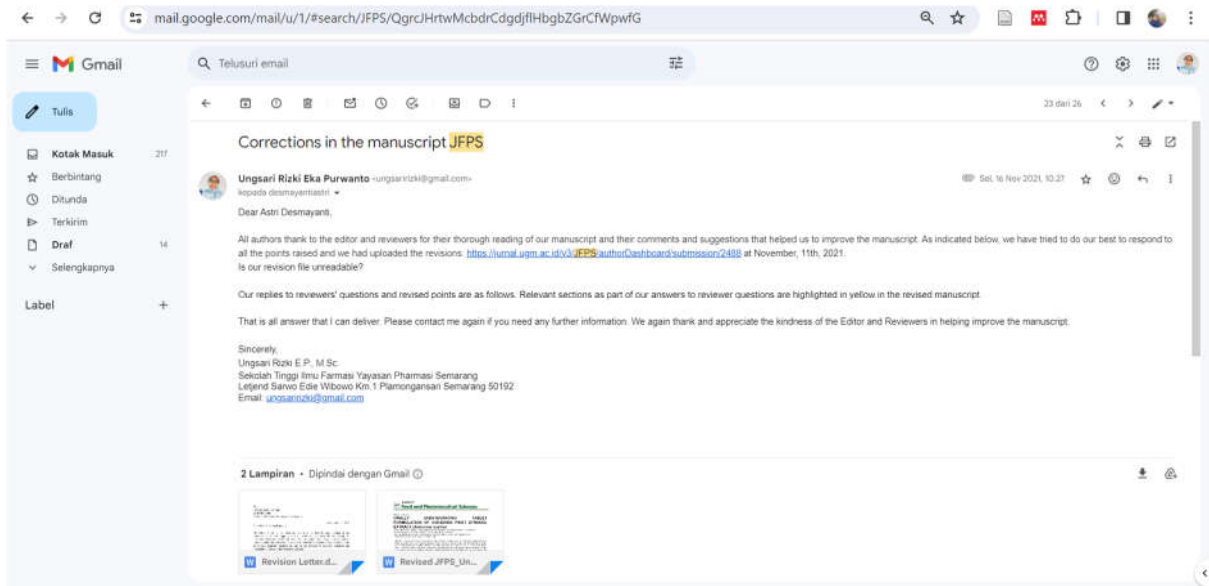
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1 Research Article

2 **ORALLY DISINTEGRATING TABLET**
3 **FORMULATION OF AVICENNIA FRUIT ETHANOL**
4 **EXTRACT (*Avicennia marina*)**

5 Ungsari Rizki Eka Purwanto¹. Maria Caecilia Nanny Setiawati^{2*}. Ika Puspitaningrum³. Siti Munisih⁴

6 Sekolah Tinggi Ilmu Farmasi Yayasan Pharmasi Semarang. Indonesia

7 *Corresponding author: *Maria Caecilia Nanny Setiawati* | Email : *caecil_nanny@yahoo.co.id*

8 Received: date; Accepted: date; Published: date

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

21 **Keywords:** *Avicennia*. Crospovidone, Starch, Orally, Disintegrating_Tablet, Antidiabetic_mellitus

23 **1. INTRODUCTION**

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

33 Most of the elderly with diabetes mellitus in Indonesia are aged 60-74 years (83.3%) who have a
34 decreased ability to swallow drugs. In addition, antidiabetic drugs are expected to be able to produce
35 fast action, so that it can reduce blood sugar levels immediately. An antidiabetic drugs are expected
36 to be able to produce fast action, so that they can immediately lower blood sugar levels. Therefore, a
37 tablet formulation that is capable of disintegrating rapidly is needed. One alternative dosage form is

38 Orally Disintegrating Tablet (ODT) or often called Fast Disintegrating Tablet (FDT), which is one of
39 the technological innovations in the field of formulation technology.

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

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

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

56

57 2. MATERIALS AND METHODS

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

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

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

70 The ingredients for the manufacture of Avicennia fruit ethanol extract were Avicennia fruit and
71 96% ethanol. The ingredients for the tablet formula were Avicennia fruit ethanol extract, mannitol,
72 avicel PH 102, starch 1500, crospovidone, Mg-stearate, talcum, aspartame and apple flavor.

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

78 2.1 Preparation of Avicennia Fruit Ethanol Extract

79 The fruit of Avicennia was cleaned of impurities by using clean water. The cleaned fruit was
80 then dried in a drying cabinet at 50°C until dry. The dried simplicia was then blended and sifted.

81 Avicennia fruit powder was macerated with 1 liter of 96% ethanol for 5 days, until the filtrate was
 82 clear. The filtrate from this filtration was combined and evaporated with a rotary evaporator until a
 83 thick extract was obtained. Furthermore, the viscous extract obtained was subjected to phytochemical
 84 screening tests including preliminary and confirmatory tests for secondary metabolites of flavonoids,
 85 alkaloids, tannins, saponins and steroids.

86 2.2 Formulation and making ODT containing Avicennia Fruit Ethanol Extract

87 ODT preparation of Avicennia fruit ethanol extract was carried out by direct compression
 88 /method. All ingredients in each formula (Table 1), except Mg stearate and talcum were mixed until
 89 homogeneous. After the mass was homogeneous, it was then mixed with Mg stearate and talcum for
 90 5 minutes. Tablet mass testing included humidity and flowability. The homogeneous mass was then
 91 tableted with a Maksindo TBL-55 single punch tablet machine. Tablets were printed with an average
 92 weight of 100 mg.

93 **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%

94

95 2.2.1 ODT Print Mass Testing

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

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

104 2.2.2 ODT Quality Testing

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

112

113

114 **3. RESULTS AND DISCUSSION**

115 Direct compression method was used in this study to produce ODT containing Avicennia Fruit
 116 Ethanol Extract, because the method of direct compression provides a disintegrating faster than with
 117 the wet granulation method. Avicel PH 102 was used as filler-binder and combined with mannitol as
 118 a filler, so as to form the desired tablet size. Avicel PH 102 was chosen because it has a larger particle
 119 size than Avicel PH 101, so that the resulting flowability is better than Avicel PH 101 which has a
 120 smaller particle size. In addition, Avicel PH 102 is also widely used as a filler-binder in the
 121 manufacture of tablets using the direct compression method. A combination of Avicel PH 102 and
 122 mannitol was also made, with the aim of masking the bitter taste of the ethanol extract of avicennia.

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

132 *3.1 The Result of Mass Print of ODT containing Avicennia Fruit Ethanol Extract*

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

139 **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

140 *FI : Starch 1500 10%, Crospovidone 0%*

141 *FII : Starch 1500 0%, Crospovidone 10%*

142 *FIII : Starch 1500 7%, Crospovidone 3%*

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

153 The results of the moisture test of the print mass mixture showed that the formula with
 154 superdisintegrant Starch 1500 was higher than the formula with Crospovidone and its combination.
 155 High humidity would make the powder mixture moist and causing the powder to not be free flowing
 156 and would stick in die and punch of the tablet machine. Pregelatinized starches, such as Starch 1500
 157 are polysaccharides containing glucose monomers in various forms linked by α -1.4 bonds. The
 158 glucose units in starch made it have a highly hydrophilic hydroxyl group. Pregelatinized starch
 159 (Starch1500) has a high LOD, but has the lowest water activity and therefore the highest ability to
 160 bind water molecule, including water molecules in air humidity [11]. This is linear with the results of
 161 the humidity test which shows that the formula with the highest Starch1500 has the highest humidity.

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

166 3.2 The Result of Quality Testing of ODT containing Avicennia Fruit Ethanol Extract

167 **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

168 FI : Starch 1500 10%, Crospovidone 0%

169 FII : Starch 1500 0%, Crospovidone 10%

170 FIII : Starch 1500 7%, Crospovidone 3%

171 Positive Control : Ondavell® 8 mg ODT

172 The filling volume used in this tableting process was set to a weight of 100 mg by adjusting the
 173 bottom punch of the tableting machine. The Indonesian Pharmacopoeia III states that tablets
 174 weighing 26-150 mg should not contain more than two tablets that deviate by more than ten percent
 175 (90-110 mg) and no more than one tablet with a deviation of more than 20% (80mg-120mg). The
 176 results of this study as listed in table 3, all tablets produced met the specified requirements.

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

182 The tablet hardness test showed that Crospovidone was a hygroscopic superdisintegrant so that
 183 it easily absorbs moisture and caused the tablet to have a low hardness causing the tablet to
 184 disintegrate quickly. Starch 1500 is a brand of pregelatinized maize starch being recommended as a
 185 disintegrant at proportions of 5–10%. It is considered a hygroscopic material with high water content,
 186 loss on drying 15% [13]. This was what caused the moisture content in the ODT mass print before
 187 tableting in FI was the highest compared to other formulas. However, the disintegration time showed

188 that the formula with the fastest disintegration time was the formula with the superdisintegrant
 189 crospovidone (FII), not combination starch and crospovidone. This was because Starch 1500 had a
 190 lower water sorption capacity than crospovidone. Starch 1500 has a maximum water sorption of
 191 about 32%, while crospovidone has a maximum water sorption of 60% [13]. Also seen from the value
 192 of water activity, Starch 1500 has an a_w value of 0.32 [14], while crospovidone has an a_w value of 0.7384
 193 [15].

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

202 **Table 4. Statistical Test Results of Physical Characteristics of ODT Containing Avicennia Fruit**
 203 **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

204
 205 Ondavell® ODT was used as a positive control as a comparison of the resulting product with
 206 products already on the market. When compared with the positive control, Avicennia Fruit Ethanol
 207 Ectract ODT product was significantly different, especially in the hardness test, wetting time and
 208 disintegration time. The results of the Post Hoc test showed that the hardness and disintegration time
 209 between the FI, FII and FIII groups were not significantly different, but compared to the positive
 210 control group they were significantly different. In general, the higher hardness value in the tablet will
 211 affect lowering disintegration time. This can be seen in the disintegration time of FI with only Starch
 212 1500 having the highest disintegrant value compared to single crospovidone and its combination
 213 with crospovidone. The degree of gelatinization can also affect the water absorption rate. Fully
 214 gelatinized starch may show slower water uptake, and it is known that the gelatinization degree of
 215 Starch 1500 was 87.7% and it was a high degree[16]. Avicennia Fruit Ethanol Extract ODT products
 216 were indeed slower to wet and disintegrate than Ondavell® ODT products. However, when
 217 compared to conventional Avicennia Fruit Ethanol Extract tablets from previous studies, the
 218 disintegration time of Avicenna ODT products was faster, it was known in previous studies that
 219 formulating Avicenna tablets produced a disintegration time of 6.61 minutes [17].

220 The results of the Post Hoc test for the wetting time test showed that there were differences not
 221 only in the Avicenna ODT tablet group with Ondavell® ODT alone, but in the FI and FII (p value :
 222 0.000) groups as well as the FII and FIII (p value : 0.000). Avicenna ODT tablets had a significant
 223 difference in wetting time. In Table 5 showed that the tablet group with only Starch 1500 disintegrant
 224 had the fastest wetting time than the single crospovidone group or the group with Crospovidone

225 combination. This was because pregelatinized starch itself has more functional groups (Picture 2) to
 226 bind to water [18] compared to crospovidone (Picture 3), so pregelatinized starch was wetted faster
 227 but has a longer disintegration time, due to the water sorption of Starch 1500 was lower than
 228 Crospovidone. Crospovidone also has a wicking mechanism so that the disintegration time was
 229 quicker. Wicking is the ability of the tablet to absorb water when placed into a liquid so that it will
 230 make the particle bonds loosen and causing it to break [19].

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

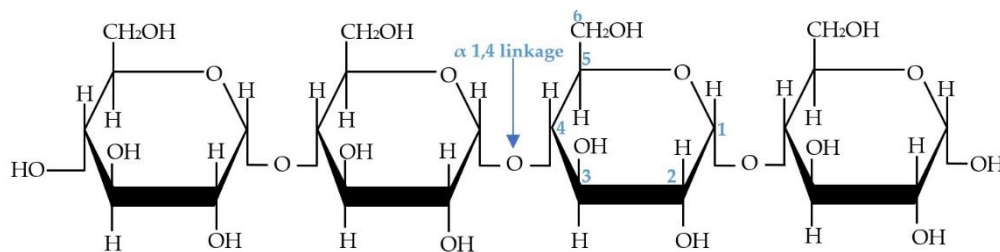
Number of Replication	Wetting time (second)			
	FI	FII	FIII	Control Positive
1	23	45	37	5.85
2	20	64	27	5.72
3	24	66	31	4.74
Average	22,33±2,08	58,33±11,09	31,67±5,03	5,43±0,61

232 FI : Starch 1500 10%, Crospovidone 0%

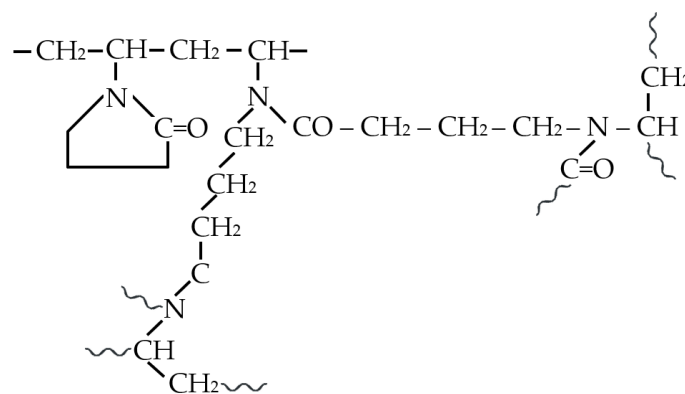
233 FII : Starch 1500 0%, Crospovidone 10%

234 FIII : Starch 1500 7%, Crospovidone 3%

235 Positive Control : Ondavell® 8 mg ODT



242 **Picture 2. Segment of An Amylose Molecule of Pregelatinized Starch [18]**



253 **Picture 3. Crospovidone Structure [20]**

254

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

261

262 **4. CONCLUSION**

263 The ethanol extract of *Avicennia* (*Avicennia marina*) fruit was successfully formulated into Orally
264 Disintegrating Tablet (ODT) preparations by varying the superdisintegrant Starch 1500 and
265 Crospovidone.

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

271

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275

276 **Conflicts of interest**

277 The authors declare no conflict of interest.

278

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Bukti copyediting :

The screenshot shows the author dashboard for the submission 'Orally Disintegrating Tablet Formulation of Avicennia Fruit Ethanol Extract (Avicennia marina)'. The 'Copyediting' tab is selected. The 'Copyediting Discussions' section is empty, showing 'No Items'. The 'Copied' section contains one entry: a document named 'astridesmayanti92, [2] Ungsari Rizki Eka Purwanto 487-495.docx' dated November 29, 2021, with the content type 'Article Text'.

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