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Formulation of Fast Disintegrating Tablet Paracetamol Employing Selected Super-disintegrant

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ABSTRACT

The objective of this research was to investigate paracetamol FDT formula with potato starch and xanthan gum or glycine or ac di sol combination that can produce the best tablet quality. The tablets were prepared by direct compression technique. Superdisintegrant such as Glycine, Ac di sol, Xanthan Gum, and Potato Starch Extract was optimized as 1-19 % on the basis of least disintegration time. Binders such as HPMC were optimized along with optimized superdisintegrant concentration. 3,5% HPMC was selected as optimum binder concentration on the basis of least disintegration time. Granule parameters included in the analysis were flowability, angle of repose, Carr's index, Hausner's ratio, and loss on drying (LOD). Tablet parameters included in the analysis were hardness, friability, disintegration time, dissolution, wetting time, and absorption ratio. The result was analyzed by Design Expert 11.1.0.1 program to decide the combination of superdisintegrant that can provide the best tablet qualities. The result showed that potato starch 15.162% and xanthan gum 4,838%, potato starch 15,050% and glycine 4,950%, and potato starch 18.390% and ac di sol 1.610%. Combination of superdisintegrant that can provide the best tablet qualities. It was concluded that, by employing commonly available pharmaceutical excipients such as superdisintegrants, hydrophilic and swellable excipients and proper filler, a fast disintegrating tablet of Paracetamol in tablet dosage form, were formulated successfully with desired characteristics.

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INTRODUCTION

Paracetamol is a para-aminophenol derivative which has an analgesic and antipyretic effect and is slightly anti-inflammatory. The efficacy of paracetamol is very commonly used to treat fever, headaches, and mild to moderate pain (Sweetman, 2009). Paracetamol is widely available in syrup preparations for use in children. Even though it has a dosage form that is easily consumed by children, if its use is not appropriate it can cause unwanted effects. To overcome this problem, there are now many studies on fast disintegrating tablets (FDT) that are suitable for pediatric patients. Practical and safe drug dosage forms, also easy to carry make the tablet popular with most patients. FDT can disintegrate in the mouth in less than a minute or even faster only with the help of a little water (Fu *et al.*, 2004).

Superdisintegrants that can be used in making FDT tablets are of various types, one of which is the starch group.Starch is often chosen because of its inert nature and its relatively cheap price (Rollando et al., 2019). Potato starch is one of the starch which is often used as a superdisintegrant in making tablets. The use of potato starch as superdisintegrant and K30 PVP as a binder in paracetamol tablets can produce% dissolution reaching 92.50%.Potato starch has a better ability as a tablet disintegrant when compared to the use of microcrystalline cellulose as a disintegrant.

Besides potato starch, other ingredients can also be used as superdisintegrants.The use of glycine in the FDT formulation can also accelerate the destruction of tablets. This is triggered by the natural nature of glycine which is easily wetted. The previous research explained that glycine combined with carboxymethylcellulose (NS-300) has the potential to improve the disintegration profile of tablets containing water-insoluble drug compounds such as ethenzamide (Fukami et al., 2006).Tablets using ac di sol as super disintegrant by direct press method has a better disintegration time when compared to tablet making using extra granular and intra-granular methods (Nazmi et al., 2013).Other studies regarding modification of xanthan gum as hydrophilic excipient disintegration for roxithromycin fast disintegration tablets showed that the percentage of modified xanthan gum used as disintegrant on low roxithromycin tablets and xanthan gum was biodegradable, so that swelling in tablets was directly compressible and dynamics could be used as hydrophilic excipients for tablets quickly destroyed with a range of 14-29 seconds (Sharma and Pathak, 2014).

MATERIALS AND METHODS

Potatos were purchased from Pasar Mergan, Malang, East Java. Aquadestwas purchased from Panadia Laboratory, Malang. H_2O_2 30% was purchased from Makmur Sejati, Malang. Potato starch reference standard (food grade) was purchased from Prima Rasa. Paracetamol, paracetamol p.a., mannitol, glycine, sodium lauryl sulfate, talc, HPMC, aspartame, KH_2PO_4, NaOH, liquid paraffin, and sunset yellow were purchased from Duta Jaya, Malang. Tisu lensa (Kimwipes), cotton fabricand filter paper.

Preparation of Potato Starch Extract

Potatoes washed, cut, added distilled water, then blended. The filtrate is filtered with a cotton cloth and then washed with distilled water. The residue was soaked with H_2O_2 6% for 30 minute while stirring using a stirrer to fade the color of starch. The residue was washed again with distilled water until the residual pH showed a value of 7. The residue was heated at a temperature of 50 °C to dry.

Evaluation of Potato Starch Extract

The composition of superdisintegrant showed in Table 1. At first the potato starch extract was observed microscopically with magnifications of 4, 10, 40, and 100 times and carried out shooting. In addition, a number of potato starch extracts and comparison standards were each analyzed using an infrared spectrophotometer at wavelengths between 4000 and 400 cm^{-1}.

Preparation of Granules

Mixed all ingredients as in Table 2 which has been sifted using 40 mesh except lubricant for 20 minutes. Powder mixing was carried out for 20 minutes. The powder mixture is then added aquadest gradually until the granule mass is formed. The granule mass is then reduced in size using a rotary granulator. The wet granules formed are then dried using an oven at a temperature of 50°C to dry.

Evaluation of Granules

The granules were evaluated for particle size distribution, flowability and angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, porosity, loss on drying (LOD), and uniformity of content.

Preparation of Tablets

Granules mixed with lubricant for 3 minutes. The granules were then removed and then pressed with a single-punch tablet press machine.

Evaluation of Tablets

Tablets were evaluated including the uniformity of weight, thickness, content uniformity, hardness, friability, disintegration time, dissolution, wetting time and absorption ratio.

Dissolution

Tablet dissolution test using apparatus 2 (paddle) 50 rpm, using 900 ml phosphate buffer pH 5.8 as dissolution medium at 37 °C. Solution was taken at 0, 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 minutes and immediately replaced with the same amount of phosphate buffer. The sample was then measured by UV-Vis spectrophotometer at a wavelength of 243 nm. No less than 80% (Q) dissolved within 30 minutes.

Wetting Time and Absorption Ratio (AR)

This test is carried out with a 6.5 cm petri dish medium inside which is given a lens paper. Petri dishes were given 6 mL of water containing 0.1 gram of sunset yellow. FDT is slowly placed on filter paper. The time needed for the entire surface of the colored tablet is wetting time. AR can be calculated using the following formula, where W_a and W_b are respectively tablet weights before and after testing.

$$AR = \frac{W_b - W_a}{W_a}$$

Analysis of Data

Analysis of granule and tablet test results with the help of the Design Expert 11.1.0.1. application. then there will be a comparison of the composition of superdisintegrants which can give the desired disintegration time. The composition is then made and tested for the quality of granules and tablets as stated above. The next test results will be compared with the results of calculations by the application.

RESULTS AND DISCUSSION

Preparation of Potato Starch Extract

Making potato starch extract involves a bleaching process using 6% H_2O_2. It aims to improve the color of potato starch from gray to white so that it is expected not to interfere with the appearance of the tablet. About 1 kg of peeled and washed potatoes can produce 60 – 70 g of potato starch.

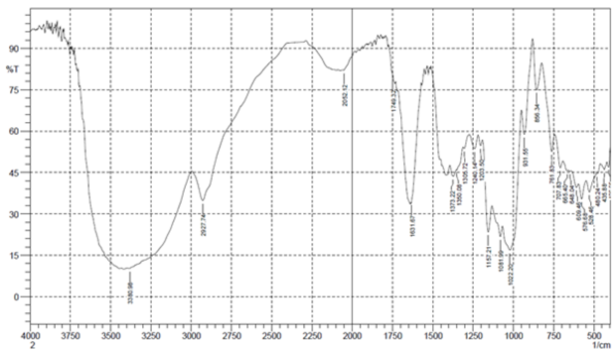

Figure 1: Spectra of potato starch extract

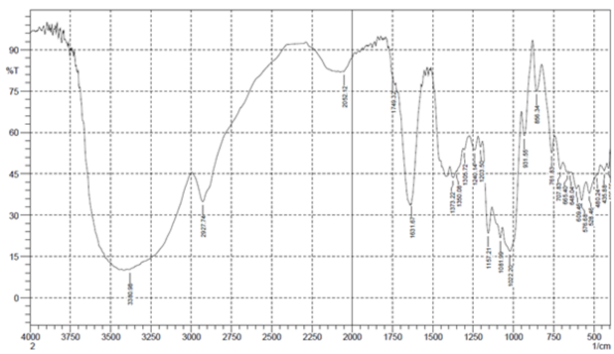

Figure 2: Spectra reference standar of potato starch (food grade)

Evaluation of Potato Starch Extract

Potato starch has a bond between C–H, C–C, C–O atoms and the bonds between O–H atoms. The

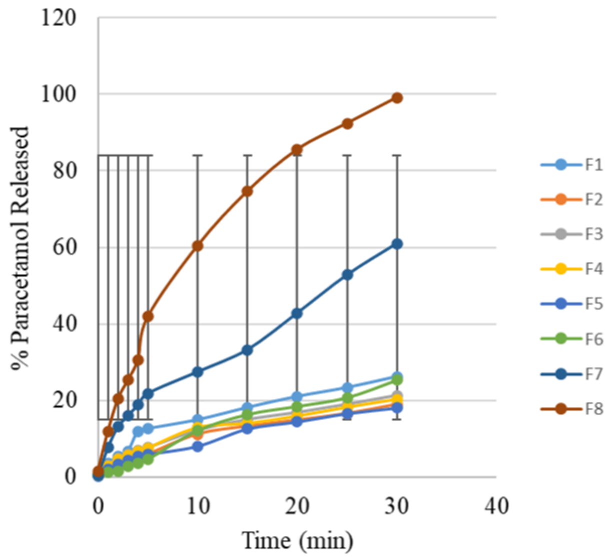

Figure 3: Dissolution Rate Evaluation of Paracetamol FDT with Combination of Potato Starch with Xanthan Gum

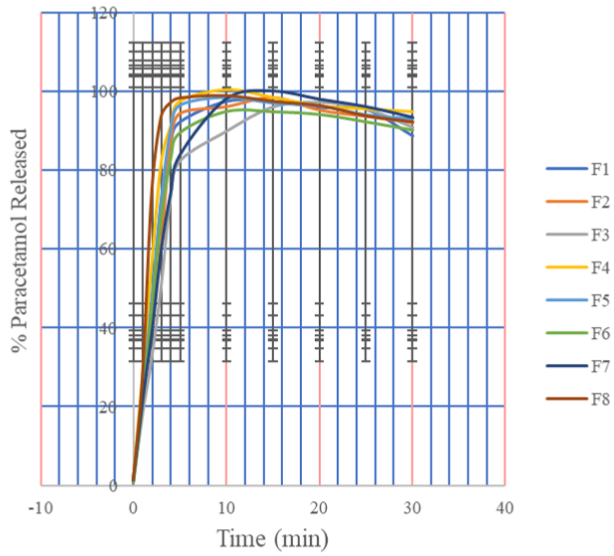

Figure 4: Dissolution Rate Evaluation of Paracetamol FDT with Combination of Potato Starch with Glycine

peak value obtained in the sample compared to the standard shows a similar result which can be seen in Figure 1, where in the sample shown in Figure 2 there is a peak with a wavelength of 700 cm^{-1}– 800 cm^{-1}which illustrates the existence of a bond between C–O, peak at wavelength 2927,24 cm^{-1}which describes the existence of a bond between C–H atoms, peak at wave 1373,22 cm^{-1}which describes the presence of aromatic groups and peaks at a wavelength of 3380,98 cm^{-1}which describes the existence of bonds between O–H atoms. The results of the peak interpretations obtained illustrate that the

Table 1: Composition of Super disintegrant

Kode Formula	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Glycine (%)								
Ac di sol (%)	1	1	2	3	3	4	5	5
Xanthan Gum (%)								
Potato starch extract (%)	19	19	18	17	17	16	15	15

Table 2: Formulation of Fast Disintegrating Paracetamol

Materials	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)
Paracetamol (50%)	125	125	125	125	125	125	125	125
Mannitol (19%)	47,5	47,5	47,5	47,5	47,5	47,5	47,5	47,5
Potato starch extract	47,5	47,5	45	42,5	42,5	40	37,5	37,5
Glycine								
Ac di sol (%)	2,5	2,5	5	7,5	7,5	10	12,5	12,5
Xanthan Gum (%)								
Sodium lauryl sulfate (1,5%)	3,75	3,75	3,75	3,75	3,75	3,75	3,75	3,75
Talc (5%)	12,5	12,5	12,5	12,5	12,5	12,5	12,5	12,5
HPMC (3,5%)	8,75	8,75	8,75	8,75	8,75	8,75	8,75	8,75
Aspartame (1%)	2,5	2,5	2,5	2,5	2,5	2,5	2,5	2,5
Total	250	250	250	250	250	250	250	250

Table 3: Flow ability and Angle of Repose Evaluation of Paracetamol FDT

Formula Code	Potato Starch and Xanthan Gum		Potato Starch and Glycine		Potato Starch and Ac Di Sol	
	Flow rate (g/s)	Angle of repose (°)	Flow rate (g/s)	Angle of repose (°)	Flow rate (g/s)	Angle of repose (°)
F_1	7.042 ± 0.056	33.562± 1.165	8.525 ± 0.209	31.692 ± 1.849	12.213 ± 0.748	32.082 ± 0.941
F_2	6.495 ± 0.090	35.280 ± 1.752	9.264 ± 0.375	31.234 ± 0.552	8.677 ± 0.068	33.687 ± 1.192
F_3	7.512 ± 0.274	31.109± 1.443	9.749 ± 0.349	30.466 ± 0.561	7.071 ± 0.038	29.150 ± 0.947
F_4	7.775 ± 0.152	32.310 ± 1.363	8.348 ± 0.192	32.861 ± 1.207	6.448 ± 0.174	28.361 ± 0.677
F_5	7.816 ± 0.211	34.725 ± 1.807	8.482 ± 0.119	29.665 ± 1.237	10.807 ± 0.309	32.996 ± 0.158
F_6	7.674 ± 0.110	33.103 ± 2.232	8.300 ± 0.107	29.376 ± 1.603	6.987 ± 0.136	28.961 ± 0.812
F_7	8.205 ± 0.230	36.078 ± 0.423	8.384 ± 0.221	29.632 ± 0.633	9.608 ± 0.341	30.810 ± 3.203
F_8	6.870 ± 0.077	29.716 ± 2.776	8.377 ± 0.044	29.351 ± 1.114	5.938 ± 0.031	27.192 ± 0.785

Table 4: TrueDensity and Carr's Index Evaluation of Paracetamol FDT

Formula Code	Potato Starch and Xanthan Gum		Potato Starch and Glycine		Potato Starch and Ac Di Sol	
	True Density (g/ml)	Carr's Index (%)	True Density (g/ml)	Carr's Index (%)	True Density (g/ml)	Carr's Index (%)
F_1	1.529 ± 0.042	13.184 ± 0.963	1.754 ± 0.060	18.972 ± 1.482	1.565 ± 0.018	14.647 ± 1.037
F_2	1.359 ± 0.087	14.647 ± 1.037	1.724 ± 0.074	17.461 ± 0.954	1.473 ± 0.039	15.568 ± 1.157
F_3	1.465 ± 0.019	13.790± 1.127	1.633 ± 0.095	16.761 ± 0.741	1.422 ± 0.012	13.237 ± 0.167
F_4	1.419 ± 0.059	15.608 ± 1.549	1.514 ± 0.101	16.658 ± 0.858	1.478 ± 0.017	13.790± 1.127
F_5	1.400 ± 0.096	15.568 ± 1.157	1.766 ± 0.080	14.126 ± 0.919	1.506 ± 0.030	15.538 ± 1.096
F_6	1.404 ± 0.107	15.538 ± 1.096	1.871 ± 0.075	13.946 ± 0.789	1.487 ± 0.044	15.211 ± 1.167
F_7	1.439 ± 0.044	13.237 ± 0.167	1.751 ± 0.143	14.524 ± 1.100	1.447 ± 0.022	13.184 ± 0.963
F_8	1.352 ± 0.116	15.211 ± 1.167	1.792 ± 0.049	16.463 ± 0.645	1.373 ± 0.037	15.608 ± 1.549

Table 5: Ratio Hausner and Porosity Evaluation of Paracetamol FDT

Formula Code	Potato Starch and Xanthan Gum		Potato Starch and Glycine		Potato Starch and Ac Di Sol	
	Hausner's Ratio	Porosity (%)	Hausner's Ratio	Porosity (%)	Hausner's Ratio	Porosity (%)
F_1	1.152 ± 0.013	72.710 ± 1.079	1.234 ± 0.022	79.374 ± 0.702	1.122 ± 0.013	76.407 ± 0.328
F_2	1.172 ± 0.014	71.792 ± 2.030	1.212 ± 0.014	78.273 ± 1.433	1.158 ± 0.014	74.676 ± 0.868
F_3	1.160 ± 0.015	71.738± 0.636	1.201 ± 0.011	77.923 ± 1.613	1.162 ± 0.025	72.048 ± 0.505
F_4	1.185 ± 0.022	70.595 ± 1.210	1.120 ± 0.012	74.502 ± 2.062	1.154 ± 0.018	75.380 ± 0.506
F_5	1.157 ± 0.016	69.269± 2.049	1.164 ± 0.012	78.114 ± 0.514	1.199 ± 0.015	74.624 ± 0.252
F_6	1.184 ± 0.015	70.995 ± 2.477	1.162 ± 0.011	78.677 ± 0.668	1.122 ± 0.026	74.283 ± 0.494
F_7	1.152 ± 0.002	69.291 ± 0.832	1.170 ± 0.015	76.738 ± 2.088	1.204 ± 0.028	70.787 ± 0.082
F_8	1.180 ± 0.016	69.866 ± 2.654	1.197 ± 0.009	79.192 ± 0.529	1.179 ± 0.047	72.149 ± 0.494

Table 6: Wetting Time and Absorption Ratio (AR) Evaluation of Paracetamol FDT

Formula Code	Potato Starch and Xanthan Gum		Potato Starch and Glycine		Potato Starch and Ac Di Sol	
	Wetting time (hour)	AR (%)	Wetting time (second)	AR (%)	Wetting time (hour)	AR (%)
F_1	10.037 ± 0.025	46.028 ±3.435	>16609.000	38.877 ± 3.837	7.257 ± 0.038	45.507 ± 0.163
F_2	13.897 ± 0.270	52.166 ± 4.862	>15836.000	41.779 ± 1.699	7.247 ± 0.040	44.985 ± 0.366
F_3	10.030 ± 0.010	65.542 ± 5.272	8612.333 ± 61.857	43.661 ± 1.682	6.557 ± 0.035	44.095 ± 0.573
F_4	10.180 ± 0.195	91.727 ± 8.176	4044.333 ± 343.008	46.747 ± 2.397	6.323 ± 0.032	44.291 ± 0.225
F_5	14.273 ± 0.065	87.475 ± 3.770	3468.333 ± 312.212	46.240 ± 3.620	6.360 ± 0.026	44.119 ± 0.967
F_6	10.200 ± 0.079	63.553 ± 5.190	1180.667 ± 62.132	49.342 ± 2.096	6.123 ± 0.025	43.938 ± 0.673
F_7	10.083 ± 0.031	69.955 ± 3.527	92.000 ± 4.582	51.368 ± 0.574	5.447 ± 0.015	43.069 ± 0.452
F_8	14.533 ± 0.060	64.268 ± 5.759	126.000 ± 7.937	50.321 ± 0.711	5.557 ± 0.006	43.782 ± 0.979

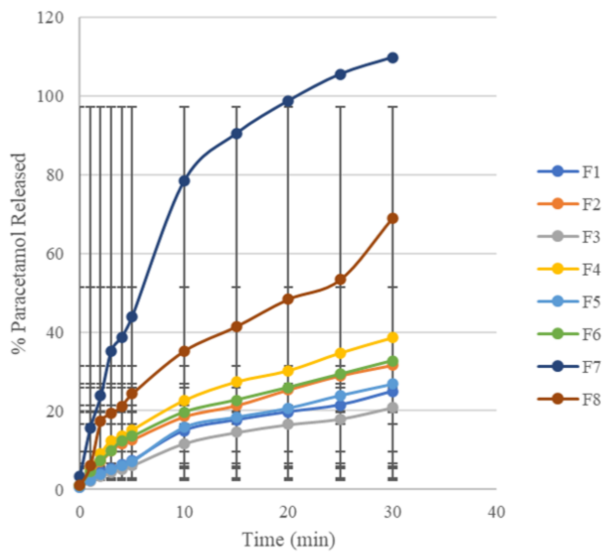

Figure 5: Dissolution Rate Evaluation of Paracetamol FDT with Combination of Potato Starch with Ac Di Sol

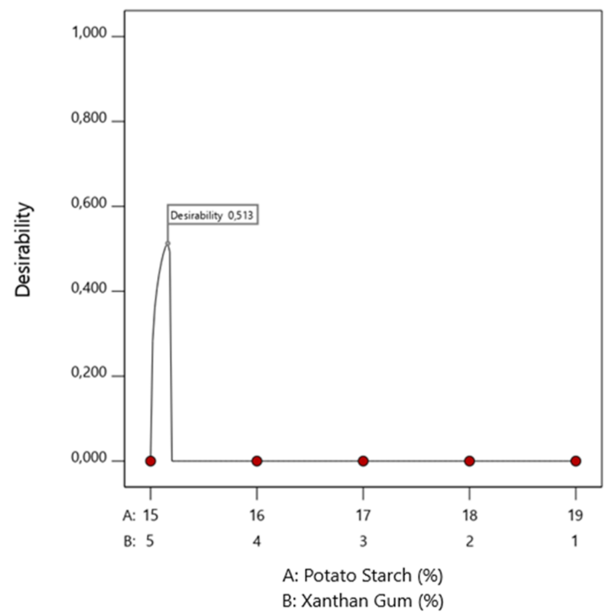

Figure 6: Desirability of Optimum Formula Potato Starch with Xanthan Gum

qualitative tests carried out showed similar results between the standard potato starch and samples and IR spectra showed that IR spectra were in accordance with the molecular structure of potato starch (Field *et al.*, 2007).

Particle Size Distribution

The results of distribution of granule size does not represent bells which means that the distribution of granules is abnormal. The problems that occur can be due to the inconsistent granulation process where the addition of distilled water is not as much as one formulation with another formulation which causes the consistency of different granules which causes the size of the resulting granule to be different between each formulation. The size of the granule that is not homogeneous can have an impact on the flow of the granule which is not good or the physical appearance of the granule itself. Furthermore,

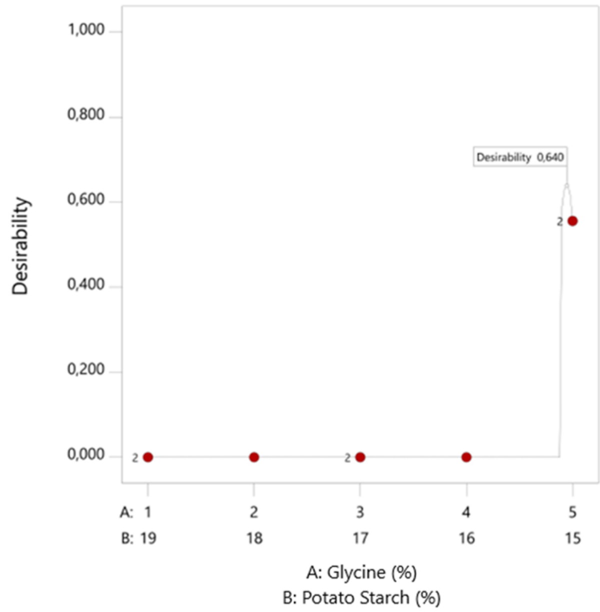

Figure 7: Desirability of Optimum Formula Potato Starch with Glycine

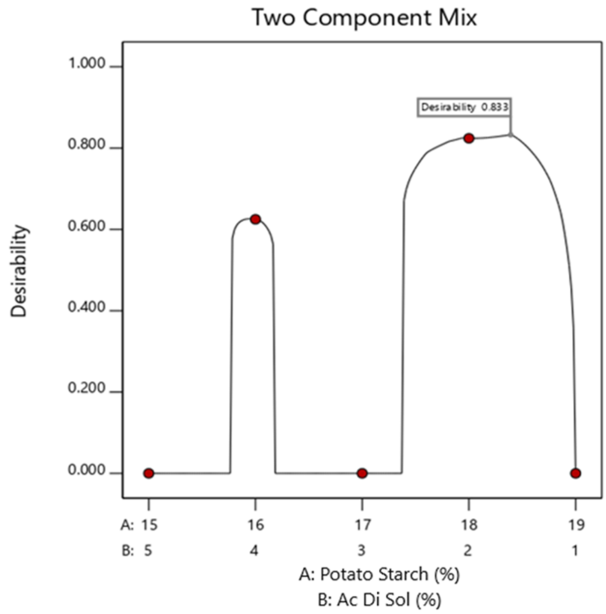

Figure 8: Desirability of Optimum Formula Potato Starch with Ac Di Sol

the poor flow of power can have an impact on the uniformity of the active ingredient in the tablet.

Flowability and Angle of Repose

The flow rate of granules with superdisintegrant combinations of potato starch with glycine, xanthan gum or potatoes can be shown in Table 3. Based on the results, the flow rate that met the requirements of $\geq$10 g/s was found in the combination of potato starch and ac di sol formula 5 (17% : 3%) and formula 1 (19%: 1%). This can be caused due to the nature of ac di sol as superdisintegrant which has properties as a towing moisture where when the amount of ac di sol increases, the flow rate will decrease (Rowe *et al.*, 2009). The equation for the flow rate of granules generated from Design Expert 11.1.0.1 the model of extreme vertice design:

$$Y = 7.14A + 8.14B \text{ (Xanthan Gum)}$$

$$Y = 8.38A + 8.89B - 0.8903AB - 6.36AB (A - B) + 11.81AB (A - B)^2 \text{ (Glycine)}$$

$$Y = 11.91A + 9.79B - 19.07AB \text{ (Ac di sol)}$$

The angle of repose of combination of potato starch with glycine, Ac disol or xanthan gum is shown in Table 3. Combination of potato starch with glycine on F_1 and F_5 - F_8, in combination of starch and ac di sol F_3, F_4, F_6, and F_8 and combinations of potato starch and xanthan gum on F_8follow good flow properties because they include a range of 25 – 30° (Nagar *et al.*, 2011). Based on this, it is known that granules with 15% potato starch content provide a smaller stationary angle. Granules that have moderate flow properties can be caused by the size of the granule that is not evenly distributed and the bonding between large particles or poor cohesion results in large angles (Stamatopoulos *et al.*, 2016). The following equation for the silent angle of the granule produced from Design Expert 11.1.0.1 is the model of extreme vertice design:

$$Y = 33{,}32A + 36{,}13B - 11{,}94AB \text{ (Xanthan Gum)}$$

$$Y = 29{,}54A + 31{,}58B \text{ (Glycine)}$$

$$Y = 31{,}98A + 30{,}89B - 12{,}52AB \text{ (Ac di sol)}$$

Bulk and Tapped Density

The bulk density of the combination of potato starch with xanthan gum is greater, namely F_1 – F_8 around 0.382 – 0.442 g/ml. Bulk density of potato starch with glycine F_1 – F_8 0.359 – 0.405 g/ml. While the bulk density of potato starch with ac di sol F_1 – F_8 is 0.193 – 0.423 g/ml. The tapped density of combination of potato starch with glycine, xanthan gum or ac di sol ranges between 0.420 – 0.508 g/ml.

True Density and Carr's Index

The true density of granules with superdisintegrant combinations of potato starch and xanthan gum, glycine or ac di sol ranged from 1.352 – 1.766 g/ml for F_1 to F_8 as in Table 5. The Carr's index value of a combination of potato starch with xanthan gum, Ac disol or glycine is shown in Table 4. The value of potato starch with xanthan gum combination or ac di sol follows a good flow characteristic of 12 – 16% (Qiu *et al.*, 2016), whereas the Carr's index of a combination of potato starch and glycine tends to have rather good flow properties. This can be caused by the high number of fines that have an impact on the magnitude of the tapped density of the granule which in turn has an impact on increasing the Carr's index (Medina and Kumar, 2006). The following equation for Carr's index generated from Design Expert 11.1.0.1models extreme vertice design:

Y = 11.34A + 16.67B (Ac di sol)

Y = 14,59A + 17,64B (Glycine)

Y = 13.14A + 13.20B + 8.79AB – 9.08AB(A – B) (Xanthan Gum)

Hausner's Ratio and Porosity

The test results of the hausner ratio value of a combination of potato starch with xanthan gum, glycine or ac di sol shown in Table 5. Hausner's ratio of F_1 – F_8 ranged from 1.152 – 1.234. Granules have a value of less than 1.25, so it can be said to have a very good flow (Nagar *et al.*, 2011). The Hausner's ratio affects the flow of the powder in the printing process which is the better the flow, then the weight, content and size of the tablet will be uniform. The following equation for compressibility generated from Design Expert 11.1.0.1models extreme vertice design:

Y = 1.12A + 1.20B – 0.0665AB + 0.4323 AB (A – B) (Ac di sol)

Y = 1.17A + 1.21B (Glycine)

Y = 1.15A + 1.15B + 0.1211AB – 0.1280 AB (A – B) (Xanthan Gum)

The porosity value of a combination of potato starch with glycine, xanthan gum or ac di sol for F1-F8 ranged from 69.269 – 79.192%. The porosity value does not meet the requirements of conventional tablet porosity 37 – 40%. This is in accordance with the theory that FDT tends to have a high porosity level to support water absorption into the tablet. However, this high porosity will have an impact on tablet hardness. Therefore, the right pressurizing pressure of the tablet is needed so that it can compensate for high porosity but still can produce optimal FDT hardness and friability (Fu *et al.*, 2004). The porosity of a tablet can later affect the disintegration time and fragility of a tablet (Panigrahi and Beheras, 2010). The following equation for compressibility generated from Design Expert 11.1.0.1models extreme vertice design:

Y = 76.21A + 70.59B + 3.09AB – 26.91 AB(A – B) (Ac di sol)

Y = 72,58A + 69,55B (Xanthan Gum)

Loss on Drying (LOD) and Uniformity of Content

The LOD value of the granules with a combination of potato starch and ac di sol, glycine or xanthan gum for F1-F8 0.061 – 0.138%. LOD are too low (less than 3%) will reduce the adhesion between particles and cause the tablet to become brittle, but when the moisture of the granule is more than 5%, it will cause granule attachment to the tablet punch punch machine that produces the tablet into capping/picking (Gohel, 2005). The following equation for compressibility generated from Design Expert 11.1.0.1 models extreme vertice design:

Y = 0.0762A + 0.1095B + 0.00696AB (Ac di sol)

Y = 0.0811A + 0.0671B + 0.1109AB – 0.1726AB (A – B) (Glycine)

Y = 0.1324A + 0.1144B – 0.2760AB – 0.7627AB (A – B) (Xanthan Gum)

The measurement results of uniformity of content on granules with a combination of potato starch and glycine, xanthan gum or ac di sol from F_1 to F_8 containing an active ingredient of paracetamol around 115.710 – 134.744 mg. The granule can be said to meet the requirements of 90 –110% (Banker, 1970).

Uniformity of Weight and Thickness

The uniformity of the weight shown a good result from all formulations of the combination of potato starch with xanthan gum, glycine, and ac di the sol as a whole met the required weight range of $\pm$15% by weight of 250 mg tablets. The range of values obtained for the whole formulation was 253.0 $\pm$ 0.002 mg – 258.80 $\pm$ 2.016 mg where the lowest weight value was owned by FDT tablets with a combination of potato starch with xanthan gum and the highest weight was owned by FDT tablets with a combination of potato starch and ac di sol. The uniformity of tablet size shown a good result from all formulations of combinations of potato starch with xanthan gum, glycine, and ac di sol as a whole met the requirements, namely the tablet diameter not less than 1 and not more than 3 times the thickness of the tablet.

Content Uniformity

The value of uniformity of the content of the entire formulation shows that all formulations have the required content of not less than 90% and no more than 120% of the active ingredient listed on the label. If the drug level does not meet the requirements, it means that the drug does not have a good therapeutic effect and is not suitable for consumption.

Hardness and Friability

The hardness of tablets from all formulations showed results that met the requirements of tablet hardness for FDT, with a range of hardness values of 3 – 5 kg / cm^2. The value of the hardness obtained from the whole formulation is 3.285 $\pm$ 0.135-5.109 $\pm$ 0.371. The hardness value of a tablet can affect the disintegration time, wetting time, and absorption ratio of a tablet. The hardness of the tablet can be influenced by the nature of the material used, the amount of binding material, and the pressing method.

Based on the results of the analysis using the Design Expert program 11.1.0.1 the hardness value of the combination tablets of potato starch and xanthan gum is Y = 3.39A + 3.55B + 3.98AB, the glycine combination is obtained by the equation Y = 4.52A + 4.54B + 0.1475AB – 3.13AB (A – B), and the combination ac di sol with the equation Y = 3.61A + 4.32B. The coefficient value of variable A which positively illustrates that the single use of potato starch can increase the value of hardness, the coefficient value of variable B which positively illustrates that the single use of xanthan gum, glycine, or ac di sol can increase the hardness value, coefficient value of variable AB the positive value illustrates that the combination of superdisintegrants can increase the value of hardness and if the coefficient value of each variable is negative then the single use or combination of each component decreases the value of tablet hardness. The higher the value of hardness will cause the tablet to be more difficult to break.

Friability of all formulations as a whole has values ranging from 0.370 ± 0.020% -1.089 ± 0.097%. Some formulations show results that come out of the range of friability requirements which are less than 1%. Different friability values of each formulation can be caused by different moisture profiles of each formulation combination where moisture can affect the adhesion force of each particle which can affect the fragility of the tablet. Humidity levels that are poorly maintained can cause tablet hardness to decrease.

Based on the results of the analysis using the Design Expert program 11.1.0.1 the friability value of the combination tablets of potato starch and xanthan gum is obtained by the equation Y = 0.7667A + 0.4139B + 0.8731AB, the glycine combination is obtained equation Y = 1.00A + 0.9607B + 0.3199AB + 0.0132AB (A - B) – 6.00AB $(A – B)^2$, and the combination ac di sol with the equation Y = 0.7650A + 0.9915B + 0.3758AB + 0.4941AB(AB). Friability of the tablet is higher then it shows that a tablet is more easily fragile and more quickly destroyed.

Disintegration Time

The disintegration time obtained from a combination formulation between potato starch with xanthan gum and ac di sol ranged from 14,178 ± 2,516 – 32,665 ± 0.926 minutes, in which the total disintegration time of the formulation contained a combination of potato starch and xanthan gum and ac di sol do not meet the requirements for disintegration time less than 60 seconds (Table 6). Whereas the disintegration time of the combination formulation between potato starch and glycine was ranged from 44,167 ± 4.355 -184.833 ± 2,994 second where there were several formulas which did not meet the requirements of disintegration time. Disintegration time that does not meet the requirements can be caused the tablet formulation uses a binder namely HPMC where HPMC can increase the hardness value of a tablet so that it retains stronger release from a drug, but on the other hand causes longer disintegration time by forming a polymer with viscosity consistency which is high enough on the surface of the tablet so that the liquid outside the tablet environment will be difficult to absorb so that the liquid cannot wet the core of the tablet containing superdisintegrant so that ultimately the super disintegrant cannot work optimally. HPMC is also a polymer with strong binding capacity so the use of HPMC which involves the addition of water activates the binding capacity and increases the strength of the polymer (Bhowmik *et al.*, 2009). The disintegration time can be improved by the addition of mannitol which has a role in accelerating the tablet disintegration time. Mannitol closes existing pores with water-soluble polymers so that it can shorten the time of destruction of FDT. Addition of sodium lauryl sulfate can also help speed up the tablet's disintegration time. Sodium lauryl sulfate is a water-soluble surface-active agent so that it can support tablet disintegration (Parkash *et al.*, 2011).

Disolution

The dissolution percentage of tablets with a combination of potato starch and glycine content showed good results and met the requirements where the requirements for dissolved percentages of tablets were at least 80% dissolved in the number of active substances listed on the label in the 30th minute (Figure 3). Whereas for the combination formulation of potato starch with xanthan gum and ac di sol showed poor results which did not meet the requirements. Dissolution results that meet the requirements there are only one in eight formulations that exist either in combination formulations of potato starch with xanthan gum or with ac di sol (Figure 4). The low percentage of solutes can be caused by various factors including the type of excipients, the process of making granulations which causes the granules to have a form that is not evenly spread, thus affecting the rate of dissolution of tablets (Silva *et al.*, 2018).

Based on the results of the analysis using the Design Expert program 11.1.0.1, the dissolution of the combination of potato starch and xanthan gum obtained the equation Y = 26,24A + 18,92B-6,41AB-29,11AB (AB), the glycine combination obtained the equation Y = 2,53A + 4.02B + 2.15AB, and the combination ac di sol with the equation Y = 81.20A + 11.43B. The coefficient value of variable A which positively illustrates that the single use of potato starch can increase tablet dissolution, the coefficient value of variable B which positively illustrates that the single use of xanthan gum, glycine, or ac di sol can increase tablet dissolution, coefficient value of variable AB a positive value illustrates that a combination of superdisintegrants can increase tablet dissolution and if the coefficient value of each variable is negative then a single use or combination of each component decreases the dissolution value of the tablet. The higher the dissolution percentage value the better that indicates that the tablet dissolves faster and absorbs faster too (Figure 5).

Wetting Time and Absorption Ratio (AR)

The wetting time obtained from a combination formulation of potato starch with xanthan gum or ac on di sol was 5.447 $\pm$ 0.015 – 32.655 $\pm$ 0.926 hours, while the wetting time of the combination of potato starch and glycine was around 92.000 $\pm$ 4.582 seconds to >16609.000 second. The absorption ratio obtained from the whole formulation ranged from 38.877 $\pm$ 3.837 – 91.727 $\pm$ 8.176 (Table 6). The wetting time and absorption ratio are related to one another where the longer the tablet takes to be wetted as a whole, the smaller the amount of solute in a given time. Long wetting time can prove if water penetration into the matrix is slow (Silva *et al.*, 2018). Based on the results of the analysis using the Design Expert program 11.1.0.1, the wetting time of the combination tablets of potato starch and xanthan gum found the equation Y = 10.03A + 10.08B + 0.4000AB – 0.7840, the glycine combination obtained the equation Y = 163.74A + 15794.77B – 16729.57AB, and the combination ac di sol with the equation Y = 7.26A + 5.45B – 0.0914AB – 2.52AB(AB). The coefficient value of variable A which positively illustrates that the single use of potato starch can increase wetting time, the coefficient value of variable B which positively illustrates that the single use of xanthan gum, glycine, or ac di sol can increase wetting time, coefficient value of variable AB a positive value illustrates that a combination of superdisintegrants can increase wetting time and if the coefficient value of each variable is negative then a single use or combination of each component decreases the tablet wetting time. The wetting time increases indicating that the time the tablet is wetted is longer which illustrates that the water absorption ability is getting slower and getting worse.

Based on the results of the analysis using the Design Expert program 11.1.0.1 the absorption ratio value of the combination of potato starch and xanthan gum obtained the equation Y = 46.68A + 65.06B + 92.00AB, the glycine combination obtained the equation Y = 51.35A + 40.74B, and combination ac di sol with the equation Y = 43.87A + 43.11B + 3.84AB. The coefficient value of variable A which positively illustrates that the single use of potato starch can increase the absorption ratio value, the coefficient value of variable B which positively illustrates that the single use of xanthan gum, glycine, or ac di sol can increase the absorption ratio value, the coefficient value of The positive AB variable illustrates that the combination of superdisintegrants can increase the absorption ratio value and if the coefficient value of each variable is negative then the single use or combination of each component decreases the absorption ratio. The absorption ratio the higher the better the signal that the water absorption time is faster.

Analysis of Data

The results of the optimization obtained are as follows where the value of desirability from each combination of ingredients in a row for xanthan gum, glycine, and ac di sol is 0.513; 0.640; and 0.833. The optimum formula with combination of potato starch and xanthan gum is potato starch 15.162% dan xanthan gum 4.838% (Figure 6). The optimum formula with combination of potato starch and glycine is potato starch 15.05% dan glycine 4.95% (Figure 7). The optimum formula with combination of potato starch and ac di sol is potato starch 18.39% dan ac di sol 1.61% (Figure 8).

CONCLUSION

The combination of potato starch and glycine as super disintegrant is recommended on FDT formulation. Glycine which has excellent wettability can promote entry of water so it supports potato starch to swelling and the tablet is disintegrated quickly.

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Conflict of interest

The authors declare no conflicts of interest.

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