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Optimization of Fast Disintegrating Tablets Diphenhydramine HCl using Co-process of Cross-link Yellow Kepok Banana Starch, Crospovidone, and Microcrystalline Cellulose

(Optimasi *Fast Disintegrating Tablet* Difenhidramin HCl Menggunakan Modifikasi Pati Pisang Kepok Kuning, *Crospovidone,* dan *Microcrystalline Cellulose*)

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Abstract: Diphenhydramine HCl is an antihistamine drug that is available in conventional tablet form. This study aimed to produce the optimum formula for a diphenhydramine fast disintegrating tablet (FDT) using a modification of starch, crospovidone, and microcrystalline cellulose (MCC) to produce quality tablets that meet the tablet's physical requirements and tablet dissolution. Starch modification was made using a two-step method of starch cross-link, then continued with silica coprecipitation. FDT was prepared by the direct compression method. Optimisation with the simplex lattice design (SLD) model uses three components: co-process starch crosslink-silica, crospovidone, and MCC, which obtained 14 formula designs. The hardness, wetting time, disintegration time, and percent dissolution are optimisation parameters. Equations, contour plots, and desirability values were determined as the optimum formula. Based on the research results, an optimum formula was obtained with the proportion of co-process cross-link starch-silica was 56.185 mg, crospovidone at 6 mg, and MCC at 45.815 mg. The result of hardness was 5 kg, wetting time 51.061 seconds, disintegration time 63.129 seconds, and dissolution was 100.972%. The interaction of the three components reduces hardness and increases disintegration time, wetting time, and percent dissolution.

Keywords: Crospovidone, fast disintegrating tablet, microcrystalline cellulose, starch modification.

Abstrak: Difenhidramin HCl merupakan golongan antihistamin yang tersedia dalam bentuk tablet konvensional. Penelitian ini bertujuan menghasilkan formula optimum *fast disintegrating tablet* (FDT) difenhidramin HCl menggunakan modifikasi pati, *crospovidone,* dan *MCC* yang berkualitas memenuhi syarat fisik tablet dan persen terdisolusi tablet. Modifikasi pati dibuat menggunakan dua tahapan metode yaitu *crosslink* pati kemudian dilanjutkan *coprecipitation silica*. FDT dibuat dengan metode kempa langsung. Optimasi dilakukan dengan model *simplex lattice design* (SLD) menggunakan 3 komponen yaitu: *co-process* pati *crosslink-silica, crospovidone,* dan *MCC*, sehingga didapatkan 14 rancangan formula. Kekerasan, *wetting time*, waktu hancur dan persen terdisolusi sebagai parameter optimasi. Berdasarkan model SLD didapatkan persamaan untuk masing-masing parameter tersebut, *contour plot* dan nilai *desirability* sehingga dapat menentukan formula optimum. Berdasarkan hasil penelitian, didapatkan formula optimum dengan proporsi *co-process* pati *crosslink-silica* 56,185 mg, *crospovidone* 6 mg, dan MCC 45,815 mg yang menghasilkan kekerasan tablet 5 kg, *wetting time* 51.061 detik, waktu hancur 63,129 detik, dan persen terdisolusi 100,972%. Interaksi ketiga komponen berpengauh menurunkan kekerasan, meningkatkan waktu disintegrasi, meningkatkan *wetting time* tablet, serta meningkatkan persen terdisolusi.

Kata kunci*: Crospovidone, fast disintegrating tablet, microcristaline cellulose*, modifikasi pati.

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INTRODUCTION

FAST disintegrating tablet or FDT, was a solid dosage form that could disintegrate quickly without the use of water in the mouth within a few seconds[1]. Diphenhydramine HCl was a first-generation antihistamine drug that was widely used to treat motion sickness. Drugs with fast onset were needed to treat nausea and vomiting, so diphenhydramine HCl was suitable to be made in the dosage form of FDT[1]. The most important component in the formulation of FDT was super disintegrants. The combination of super disintegrant agents that could be used was kepok banana starch and crospovidone[2].

Kepok banana was a plant that was rich in 20.53% carbohydrates. Kepok bananas contain 82.69% starch, 1.01% protein, and 0.06% fat. The high starch content in kepok bananas has the potential to be used as a tablet-disintegrating agent[3]. Kepok banana (*Musa paradisiaca* L.) native starch can be used as a tablet disintegrant, which has a swelling capacity of 125%, which can affect the disintegration time of tablets[4]. The dissolution studies show that tablets containing 5-10% banana starch give 89.6-94.7% of drug release[5]. Kepok banana native starch still requires physical and chemical modification processes to produce derivatives that have better and specific pharmaceutical characteristics, especially for the manufacture of FDT tablets. Crospovidone was a synthetic cross-linked polyvinylpyrrolidone that was produced by the proliferative polymerization of vinylpyrrolidone[6]. Crospovidone has a very high capillary action mechanism, resulting in when the tablet comes into contact with the medium used quickly, it penetrates the pores of the tablet. Crospovidone was used in the range of 2-5% in tablets prepared by direct compression methods[7]. Microcrystalline cellulose (MCC) was suitable for use as a filler in the direct compression method because it has good flow and compressibility properties[7].

This research aimed to determine the effect of a combination of co-processed crosslink-silica starch and crosspovidone as a disintegrant. The crosslink-silica starch co-process was prepared in two stages, the cross-link and continued co-process, using the silica coprecipitation method on the surface of the cross-link starch particles. MCC as a tablet filler. The combination of these three ingredients needs to be optimized using the simplex lattice design (SLD) method to obtain the optimum formula for FDT diphenhydramine HCl to meet the requirements for tablet hardness, tablet disintegration time, wetting time, and percent dissolution.

MATERIALS AND METHODS

MATERIALS. The materials used in this research were Banana Kepok 90 days after flowering was collected from the Bandungan field located at Semarang, sodium bisulfite (Merck Sigma-Aldrich®, German), sodium tripolyphosphate (technical grade, Merck Sigma-Aldrich®, German), NaOH (analytical grade, Merck Sigma-Aldrich®, German), HCl (Merck Sigma-Aldrich®, German), silicon dioxide (SOLVAY Tixosil® 38A, China), Diphenhydramine HCl was purchased from Phapros pharmaceutical industry in Semarang city, Indonesia. Microcrystalline cellulose (Accent, India), crospovidone (Huangshan Bonsun Pharmaceutical, China), mannitol (Brataco Chemical, Indonesia), aspartame (Brataco Chemical, Indonesia), Mg stearate (Brataco Chemical, Indonesia), talk (Brataco Chemical, Indonesia).

Equipments. Tablet compression machine single punch (TDP-5 Single Punch Tablet Press Shanghai Pharmaceutical Machinery, Shanghai, China), flowability tester, FT-IR Spectrometer (Perkin Elmer Spectrum Version 10.4.00, Bridgeport Avenue Shelton, USA), Scanning Electron Microscope (Phenom pro-X desktop SEM with EDX, Waltham, Massachusetts, United States), and spectrometer UV-VIS double beam (Shimadzu, Kyoto, Japan).

METHODS. Starch Isolation. The banana kepok (*Musa paradisiaca L.*) was ready to harvest; green and unripened, it was collected from the Bandungan field located in Semarang. The fruit was peeled, cut into 4 mm, and each slice was cut into four pieces and rinsed immediately using sodium bisulfite solution (0.25 g/L) in proportion 2:1 (v/w) at 40ºC. The banana kepok fruit was blanded and macerated at low speed (100 rpm). The slurry was stirred and kneaded to accelerate the release of starch from the protein or gum covering it, then gradually filtered using a filter cloth. The pulp was then washed with distilled water until it became clear. The starch suspension was then precipitated for about 6-8 hours until the sediment was separated from the soaking water. The precipitated starch was washed with water 2-3 times until a white (brownish-white) starch was produced. The starch was dried at 40ºC in an oven for 48 hours, ground, and sieved through a 100 mesh screen[7].

Cross-linked Starch. The banana kepok starch (150 g) was dispersed in 225 mL of distilled water. The suspension was preheated under constant stirring at 70ºC. The mixture was added with sodium tripolyphosphate (3%) and stirred with a magnetic stirrer on a hot plate at 70ºC. The mixture was added with NaOH (0.1 N) until a pH of 10, continuously stirring

Table 1. The design of the optimisation formula FDT diphenhydramine with the SLD method.

Composition	Formula (mg)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Diphenhydramine HCl	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Co-process starch Crosslink-silica	51	6	96	6	21	96	66	6	6	51	6	51	36	21
Crospovidone	51	96	6	96	21	6	21	6	51	51	6	6	36	66
MCC	6	6	6	6	66	6	21	96	51	6	96	51	36	21
Mannitol	55	55	55	55	55	55	55	55	55	55	55	55	55	55
Aspartame	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mg Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talk	2	2	2	2	2	2	2	2	2	2	2	2	2	2

at 45ºC for 60 minutes. The starch mixture was added with HCl (1M) until a pH of 6.5. The filter was washed with distillate water. Cross-linked starch dried at 40ºC for 24 hours using an oven, was ground, and sieved using mesh sieve no. 20[8].

Cross-linked Starch-Silica Co-process. The cross-linked banana starch (50 g) was mixed with hot HCl (2M) (100 mL) (80ºC) for 60 minutes. The colloidal silicon dioxide (50 g) was dispersed in NaOH (2M) (100 mL) and distilled water (100 mL) while stirring until it was homogeneous. The cross-linked starch suspension was gradually added to the silica suspension, stirring at high speed for 1 hour at 25ºC. The pH of the mixture was kept between 6.5 and 7.0 by the adjustment with HCl during the mixing process. The product was filtered using filter paper and washed with distilled water. The co-process cross-linked starch silica was dried at 90ºC and sieved using mesh no. 40[9].

Fast Disintegrating Tablet Preparation. FDT was prepared using the direct compression method. The optimisation of the formula using the simplex lattice design model was using a ratio of a co-process of cross-linked starch-silica (A) as disintegrate, crospovidone (B) as disintegrate, and MCC (C) as filler binder, in proportions of 6–96 mg parts with a total amount of 108 mg (Table 1).

Swelling Power and Solubility of Co-process Cross-link Starch-Silica. The starch suspension (1%) was heated for 30 minutes in a water bath at 65°C with constant stirring, then chilled. The suspension was centrifuged at 3000 rpm for 15 minutes. The supernatant was decanted, and the residual volume was determined. The sediment was dried for 2 hours at 130°C. For the solubility calculation, the petri dish was weighed. To determine swelling power, the weight of the wet sediment was measured[10].

$$\text{Solubility} = \frac{\text{A}}{\text{W}} \text{X } 100\%$$

$$\text{Swelling power} = \frac{\text{D}}{\text{W } (1 - \text{S})} \text{X } 100\%$$

Note: A = weight-dry petri dish; W = weight of sample; D = weight of sediment; S=Solubility

Scanning Electron Microscopy (SEM). Samples were mounted on sluminium stubs and coated with gold by sputtering at 1200 V, 20 Ma for 105 s using a vacuum coater.

Tablets Hardness. Ten tablets were tested from each formula randomly, and their hardness was measured with the hardness tester[11]. FDT has a hardness between 3 and 5 kg/cm^2.

Wetting Time. A sheet of tissue paper was placed in a small petri dish containing 10 ml of water-soluble dye. The FDT was placed in the centre of the sheet of tissue paper. The time needed for water to reach the upper surface of the tablet was noted as the wetting time[12].

Disintegration Time. The FDT was placed in the middle of the petri dish, which was given 20 mL of distilled water[13].

Dissolution Studies. Dissolution using the USP II dissolution test apparatus was set at 50 rpm in 900 mL of distilled water as the dissolution medium. The temperature was maintained at 37±0.5ºC. Samples were taken at 0, 5, 10, 15, 20, 25, and 30 minutes. Aliquots (5.0 mL) were taken, filtered, and analysed using a Shimadzu UV spectrophotometer at 257 nm.

Data Analysis. The effect of the addition of co-process starch crosslink-silica, crospovidone, and MCC on the evaluation carried out (hardness, wetting time, disintegration, and dissolution) can be seen using Design Expert Software version 11 using the mixture simplex lattice method to obtain the simplex lattice design equation. The desirability value was used to determine the contour plot and optimal area for each response. The verification results of the programme's optimum prediction formula were carried out with a comparable formula for experimental results using one sample T-test analysis with a confidence level of 95% using SPSS 23.0 statistics.

RESULTS AND DISCUSSION

Swelling Power and Solubility of Co-process Cross-link Starch-Silica. The co-process with silicon dioxide and cross-link starch was only slightly soluble in cold water. The solubilities of co-process with silicon dioxide were higher than cross-link starch and native starch, respectively (Table 2). The water solubilities of the co-process cross-link starch-silica were 23.14%, which was higher than native banana starch, cross-link starch, SSG, and rice starch[15]. Increased solubility was observed in co-processed with colloidal silicon dioxide. Addition of colloidal silicon dioxide composition and cross-link porosity of starch by inhibiting the bonding between starch particles[15]. Increased porosity and interparticle space in the co-processed starch results in increased water penetration into the starch particles. The alkaline environment that facilitated gelatinization was created by the solubility of silicon dioxide in water.

The swelling power of the co-process with silicon dioxide was 69.02%, which was higher than cross-link starch, native banana starch, and SSG. The swelling power value of the cross-link was influenced by the addition of silicone dioxide used in the co-process. The attraction between water and the polymer of silicon dioxide increased the swelling power of co-process cross-link starch silica.

Scanning Electron Microscopy (SEM). Co-processes have a particle size of 9.24–93.9 μm (Figure 1). The small size of silica particles (236–412nm) on the surface of the cross-linked starch co-process indicates that silicon dioxide has precipitated on the surface of the cross-linked starch. It could be correlated to a decrease in the surface area of the starch-silica coprecipitate, as reported by a previous study[16].

Physicochemical Evaluation of Tablets. The hardness of the tablet was tested using the Monsanto hardness tester, and the results were in Table 3. The hardness average for all the formulations was found to be in the range of 3.04 to 4.95 Kg/cm^2, according to the limit of previous study[12]. The SLD Equation obtained for tablets hardness $Y = 3.70(A) + 3.01(B) + 4.73(C) + 1.27(A)(B) + 3.43(A)(C) + 4.22\ (B)(C) - 17.42\ (A)(B)(C)$. The equation shows Y as tablet hardness (kg), A for the concentration of Co-process cross-link starch-silica used (mg), B for Crospovidone used (mg), and C for the concentration of MCC used (mg).

The MCC coefficient value (4.73) was the most significant factor in increasing tablet hardness. The high concentration of MCC and a high hardness value were evidenced by formulas 5, 8, and 9. The MCC, co-process cross-link starch-silica and crospovidone mixture has a positive coefficient value, indicating that the mixture can increase the hardness, but the effect was not as significant as the MCC. The MCC has a rough particle surface with a low density; particles bind to each other, resulting in increased tablet hardness. According to the handbook of pharmaceutical excipients, MCC was an excipient that had good compressibility. The MCC was an excipient that was used in making tablets.

Table 2. Comparison of physical properties of kepok banana native starch, cross-link starch, and co-process cross-link starch-silica.

No	Evaluation	Native starch [14]	Cross-link starch ($\bar{x} \pm SD$)	*Co*-process cross-link starch-silica ($\bar{x} \pm SD$)
1	Solubility	14.42 – 15.49%	13.25 % ±0,94	23.14%±0.84
2	Swelling power	42.55 – 43.96%	52.24% ±0.58	69.02%±0.64

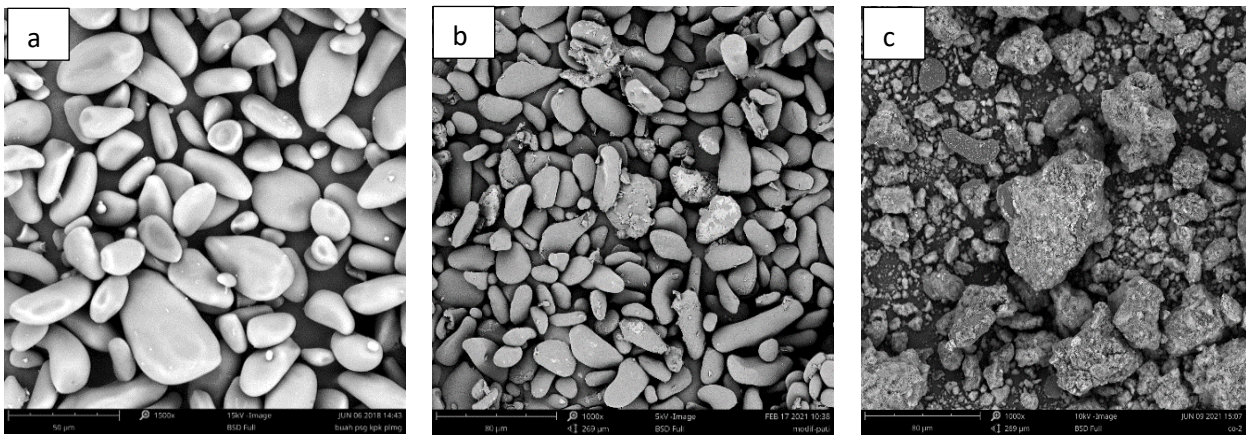

Figure 1. Scanning electron microscopy result of kepok banana native starch (a)[14], cross-link starch (b), co-process Cross-link starch-silica (c).

Its good compressibility properties can produce hard tablets with little pressure[6]. Based on the contour plot (Figure 3), the proportion of co-processed starch Crosslink-silica, crospovidone, and MCC required to produce the desired tablet hardness was 3-5 kg/cm^2.

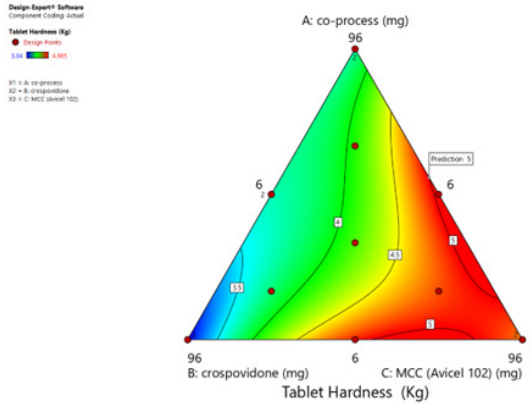

Figure 3. Contour plot tablet hardness.

The wetting time results for the FDT formulations were found to be in the range of 50–95 seconds (Table 3). All the formulas gave an acceptable wetting time (3 minutes)[17]. The maximum and minimum wetting times for Formula 4 and Formula 8 were 51.50 seconds and 94.83 seconds, respectively. The wetting time parameter was very significant for the disintegration behaviours of FDT. The SLD Equation based on wetting time data: $Y = 82.52(A) + 53.65(B) + 92.56(C) - 4.21(A)(B) - 145.53(A)(C) - 33.39(B)(C) + 171.85(A)(B)(C)$. The equation showed Y as wetting time (seconds), A was the number of co-process cross-link starch-silica used (mg), B was the number of crospovidone used (mg), and C was the number of MCC used (mg).

The coefficient value of crospovidone (53.65) was the most influential in accelerating the wetting time. In this study, the combination mixture of co-process crosslink-silica, crospovidone, and MCC has a positive coefficient value that can increase the wetting time. The amount of MCC was reported to be comparatively higher than the others, leading to the longest wetting time. The wetting time was longer for the tablet with high hardness. The porous structure of crospovidone allows water to enter the tablet, increasing the tablet's wetting time[18]. The tablet's compactness was always indicated by the increase in hardness. The increased hardness of the tablets may cause a decrease in the water penetration rate and prolong the wetting time due to their relative higher compactness. Based on the contour plot (Figure 4), a proportipon of co-process starch crosslink-silica, crospovidone, and MCC was needed to produce the desired tablet.

The disintegration time results for all formulas are presented in Table 3. Formula 12 and formula 8 were found to have minimum and maximum disintegration

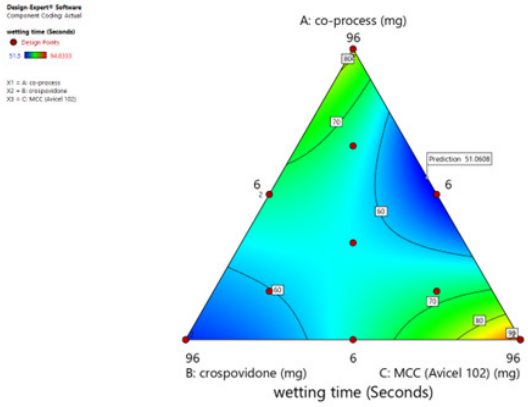

Figure 4. Contour plot of wetting time.

Table 3. Physicochemical evaluation of FDT diphenhydramine HCl.

Formula	Hardness (kg/cm^2) ($\bar{x} \pm SD$)	Wetting Time (second) ($\bar{x} \pm SD$)	Disintegration (second) ($\bar{x} \pm SD$)	Dissolution (%) (30 minutes) ($\bar{x} \pm SD$)
1	3.57 ± 0.17	65.00 ± 0.63	72.66 ± 0.51	101.41 ± 0.12
2	3.06 ± 0.15	53.50 ± 0.40	68.83 ± 0.63	92.46 ± 0.29
3	3.73 ± 0.25	87.00 ± 0.89	94.66 ± 0.8	100.55 ± 0.11
4	3.04 ± 0.08	51.50 ± 0.63	67.33 ± 0.51	95.37 ± 0.27
5	4.98 ± 0.04	61.33 ± 0.81	77.17 ± 0.98	101.78 ± 0.12
6	3.56 ± 0.29	79.50 ± 0.83	93.33 ± 0.81	100.74 ± 0.18
7	4.40 ± 0.82	59.50 ± 0.83	72.83 ± 0.98	100.95 ± 0.08
8	4.60 ± 0.52	94.83 ± 0.54	104.00 ± 0.75	101.30 ± 0.11
9	4.97 ± 0.11	64.33 ± 0.51	78.33 ± 0.51	93.68 ± 0.31
10	3.75 ± 0.25	68.33 ± 0.51	80.33 ± 0.81	101.48 ± 0.17
11	4.82 ± 0.37	92.00 ± 0.54	103.33 ± 0.81	101.47 ± 0.12
12	4.94 ± 0.15	54.33 ± 0.51	66.16 ± 0.98	100.67 ± 0.07
13	4.02 ± 0.11	65.50 ± 0.54	87.83 ± 0.98	101.40 ± 0.31
14	3.57 ± 0.49	65.00 ± 0.63	76.83 ± 0.98	95.42 ± 0.34

times of 66.16-104.00 s. The low bioavailability of the drug when administered by patients was indicated by the spontaneous or partial disintegration of tablets. The fast-disintegrant tablets must disintegrate completely in the mouth within 3 min or less, ideally within 30 s, according to previous studies[17]. The result can be observed that there was a reasonable correlation between the wetting time and the disintegration times. The SLD Equation based on the disintegration tablet: Y = 93.22(A)+68.61(B)+102.98(C)–18.83(A)(B)–139.48(A)(C)–31.63(B)(C)+393.26 (A)(B)(C). The equation showed Y as the disintegration tablet (seconds), A was the number of co-process cross-link starch-silica used (mg), B was the number of crospovidone used (mg), and C was the number of MCC used (mg).

The shorter the wetting time, the quicker the tablet disintegrates. The shorter the wetting time, the quicker the tablet disintegrates. The coefficient value of crospovidone (68.61) was the most influential in increasing the disintegration time. The crospovidone particle has a strong effect on the disintegration process, and the larger particles provide faster disintegration. The intra-particular porosity increases, leading to water uptake and increased disintegration tablet[18]. According to reports, co-process cross-link starch-silica and crospovidone had rapid capillary activity and significant hydration power but had no affinity for gel formation. Both of the super disintegrants used in our study were cross-linking agents, as should be noted. The amount of hydroxylation and cross-linking were the chemical attributes that determined the water uptake of these disintegrants. The cross-linking process makes them soluble in water and decreases the viscosity of adjacent water, resulting in greater drug release. The hydroxyl group present in these super disintegrants creates a strong hydrogen-bonded network that reduces water penetration into polymers. Based on the contour plot (Figure 5), the proportion of co-processed starch crosslink-silica, crospovidone, and MCC required to produce the desired FDT tablet disintegration time according to European pharmacopoeia was less than 3 min.

The dissolution study for all formulas was reported to be in the range of 92.46-101.48% (Table 3); this result was higher than the previous study, which reported that diphenhydramine FDT has 95% drug release[18]. For all the formulas, the dissolution exhibited a proportional relation with wetting time and disintegration time. Based on the percent dissolution data on the formula, run tablets 1-14 until 30 min, and the equation was obtained: Y=100.50(A)+93.64(B)+101.81(C)+15.83(A)(B)–0.4472(A)(C)–15.78(B)(C)+60.69(A)(B)(C). The equation shows that Y was the percent dissolution (%), A was the number of co-process cross-link starch-silica used (mg), B was the number of crospovidone used (mg), and C was the number of MCC used (mg).

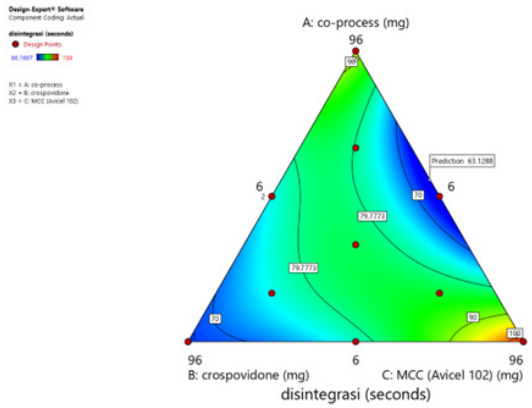

Figure 5. Contour plot of disintegration tablet.

The coefficient value of MCC (101.81) was the most influential in increasing the dissolution response of FDT tablets. The coefficient of the mixture cross-link-silica, crospovidone, and MCC has a positive value (60.69) that could increase the dissolution, but the effect was not as significant as MCC. MCC as a filler tends to have a higher percent release of the hydrophilic nature of MCC[6], which can facilitate the entry of water into the tablet and help dissolve the drug. Lignin content in MCC can increase the rate of drug dissolution[19]. Based on the contour plot (Figure 6), the proportion of co-processed starch crosslink-silica, crospovidone, and MCC needed to produce the desired percentage of dissolution of FDT tablets, namely at a 30-minute concentration of dissolved diphenhydramine HCl >80%[20].

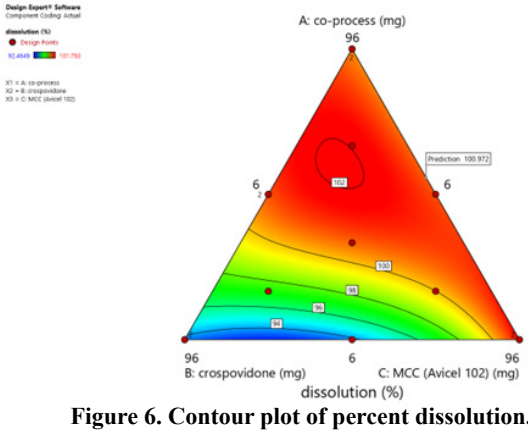

Figure 6. Contour plot of percent dissolution.

Determination of The Optimum Formula. The objective of formula optimisation was to determine the optimal composition of the factors used: co-process cross-link starch-silica, crospovidone, and MCC. Optimum formula prediction using Design Expert Software version 11. The parameters for determining the optimum formula for fast disintegrating tablets were hardness, wetting time, disintegration time,

and percent dissolution of FDT tablets that meet the requirements with a desirability value close to 1. The closer to one, the better the desirability value. The desirability value obtained based on the design expert 11.0 was 0.920 with the concentration of co-process cross-link starch-silica 56.185 mg, crospovidone 6.000 mg, and MCC 45.815 mg (Figure 7). The optimum formula for one tablet was:

R/ Diphenhydramine HCl	25 mg
Co-process cross-link starch-silica	56.185 mg
Crospovidone	6.000 mg
MCC	45.815 mg
Mannitol	55 mg
Aspartame	8 mg
Mg stearate	2 mg
Talk	2 mg

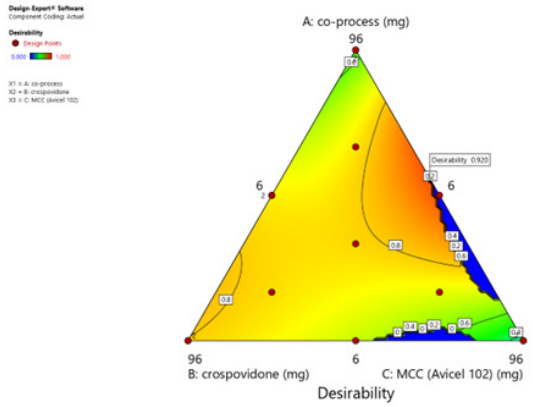

Figure 7. The desirability of the optimum formula.

The results of this study were validated by one sample T-test using SPSS 23.0 statistics. The data obtained must be tested for normality first. The optimum formula test results show that all parameters were normally distributed because the value was >0.05 (Table 4). This can be continued with the One Sample T-test. The results of each test parameter compared to the theoretical results of the SLD method show that the results were not significantly different because the significance value was >0.05 (Table 5). The optimum formula tested was based on the predictions of the SLD method in the design expert software 11.

Table 4. Tests of normality.

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Hardness tablet (kg/cm^3)	.231	5	.200*	.881	5	.314
Wetting time (sec)	.332	5	.075	.873	5	.278
Disintegration (sec)	.241	5	.200*	.878	5	.299
Dissolution (%)	.274	5	.200*	.867	5	.254

Table 5. Equation validation.

Respon	Average	Theoretical	Sig.
Hardness tablet (kg/cm^2)	4.960	5.000	0.099
Wetting time (sec)	51.062	51.06	0.866
Disintegration tablet (sec)	63.098	63.13	0.507
Dissolution (%)	100.952	100.97	0.266

CONCLUSION

The interaction between co- process starch crosslink-silica, crospovidone, and MCC can reduce tablet hardness, increase disintegration time, increase tablet wetting time, and increase dissolution percent. The optimum formula for FDT diphenhydramine HCl was co-process starch crosslink-silica 56.185 mg, crospovidone 6.000 mg, and MCC 45.815 mg, with desirability value was 0.920.

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