Optimization of sodium starch glycolate and maltodextrin in chlorpheniramine maleate Fast Disintegrating Tablet (FDT) by factorial design

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ABSTRACT: Chlorpheniramine maleate (CTM) is an antihistamine that is widely available on the market in tablet form. It needs to be formulated in the form of Fast Disintegrating Tablets (FDT) to produce a faster therapeutic effect to treat allergy symptoms, which are often irritating. The FDT contains a super disintegrant to regulate the disintegration speed of tablet and a binder to provide the ability to bind between powders. This research was conducted to obtain the effect of Sodium Starch Glycolate (SSG) as a super disintegrant and maltodextrin as a binder, and their interaction in the chlorpheniramine maleate tablet formulation. This research was categorized as true experimental designs with FDT quality parameters such as organoleptic, hardness, friability, disintegration time, wetting time, water absorption ratio, and content uniformity. The optimization method used is factorial design. Data analysis was performed using Analysis of Variance (ANOVA). Based on the data, it concludes that Sodium Starch glycolate (SSG) affects increasing hardness, increasing friability, extending disintegration time, extending wetting time, and reducing the water absorption ratio. Maltodextrin, has the effect of increasing hardness, reducing friability, extending disintegration time, extending wetting time, and reducing the water absorption ratio. The interaction of SSG and maltodextrin has the effect of reducing hardness, increasing friability, shortening disintegration time, shortening wetting time, and increasing the water absorption ratio.

KEYWORDS: Chlorpheniramine maleate; factorial design; fast disintegrating; maltodextrin; sodium starch glycolate.

▪ **INTRODUCTION**

In the last few decades, the prevalence of allergy sufferers has reached at least 30 - 40% of the population worldwide, with children and young adults as the dominant groups [1]. Chlorpheniramine maleate (CTM) is an antihistamine that is widely used to treat allergy symptoms. For now, CTM on the market can be administered in four administration routes, namely oral, intramuscular, subcutaneous, and intravenous. Oral administration, especially in tablet form, is the most popular dosage form. However, orally CTM can undergo first-pass metabolism in the liver which results in a decrease in bioavailability of 25-50% [2]. For this reason, administration of preparations in the form of fast disintegrating tablets (FDT) needs to be developed as an alternative administration. Fast disintegrating tablets (FDT) are tablets that disintegrate quickly when they come into contact with saliva in the oral cavity in less than 30 seconds. In this way, it is hoped that the drug can be dissolved and provide a faster therapeutic effect. In addition, this dosage form makes it easier for patients who have difficulty swallowing conventional tablets, such as geriatric patients and dysphagia sufferers. Also, its more practical use without the help of water, as well as the sweeter taste, are expected to increase patient compliance with taking medication [3]. The tableting method used is the direct compression method. This method is widely used and is considered the most efficient in terms of time and cost [4]. However, this method is intended for materials with good flow properties and compressibility [5]. The excipient used plays a very important role, the excipient must be able to support the preparation to disintegrate more quickly because the excipient has a greater composition than the active ingredient. The independent variables in this research are the super disintegrant and the binder. The super disintegrant used in this research is a synthetic super disintegrant such as Sodium Starch Glycolate (SSG) which is widely used in oral drug formulations. Generally, SSG is used in tablet formulations using direct compression and wet granulation methods because it has good flow properties. The binder used is maltodextrin. Maltodextrin is a modified wheat starch that can be used for direct compression, this material has good flow properties and compressibility [6]. The optimization method used is a factorial design to determine the response of each factor as well as the interactions between factors. This method has maximum efficiency in estimating effects and is

more economical in terms of the amount of materials [7]. The physical property parameters used to determine the optimum FDT preparation include tablet hardness, tablet friability, tablet disintegration time, tablet wetting time, and water absorption ratio. Testing for content uniformity is carried out only on selected formulas. This research aims to find the effect of Sodium Starch Glycolate (SSG) as a super disintegrant and maltodextrin as a binder and their interaction in the chlorpheniramine maleate tablet formulation.

▪ **MATERIALS AND METHODS**

Material

Chlorpheniramine Maleate (Sigma Aldrich®, Saint Louis, USA), working standard Chlorpheniramine Maleate (BPFI, Jakarta, Indonesia), sodium starch glycolate (Primojel®, Ahmedabad, India), maltodextrin DE 4.0 (Sigma Aldrich®, Saint Louis, USA), magnesium stearate (Faci Asia Pacific PTE. LTD, Jurong Island, Singapore), talcum (Haicheng Xinda Mining Industry CO. LTD, Haicheng, China), orange flavors (Everstyle Foodstuff Industrial CO. LTD, Taipei, Taiwan), mannitol (Shijuazhuang Huaxu Pharmaceutical CO. LTD., Shijiazhuang, China), tartrazine (Idacol®, Ahmedabad, India), carmoisine, aquadest, HCl 0,01 N.

Equipment

Analytical balance OHAUS PA 213 (Stuccler, Putian, China), porcelain cup, 18 mesh sieve, cube mixer GmbH Ar 401 (Erweka, Langen, Germany), beaker glass, mortar, stamper, tap density volumizer HY-100B (Wincom Company Ltd., Changsha, China), flowability tester GmbH (Erweka, Langen, Germany), single punch tablet (Delta, Philadelphia, USA), hardness tester YD-1R (Laboao International, Zhengzhou, China), disintegration tester Develop BJ-2 (Laboao International, Zhengzhou, China), friability tester CS-2 (Lorderan, Shanghai, China), filter paper Whatman, stopwatch, vacuum pump, spectrophotometer UVmini-1240 (Shimadzu, Kyoto, Japan), and cuvette.

FDT manufacturing method

The FDT was made by the direct compression method. Each ingredient was weighed according to the formula in Table 1. Tartrazine, SSG, and maltodextrin were weighed and blended for 15 min in a cube mixer. Then orange flavour, CTM, and mannitol were sequentially added to the mixture after 10 min of mixing. The obtained mixture was blended with magnesium stearate and talcum for 5 minutes. The tablets were compressed using a single-punch tablet compression machine at the same high compression force and speed for each formula to get a tablet of 100 mg weight containing 4 mg of chlorpheniramine maleate.

Table 1. Formula chlorpheniramine maleate FDT.

Ingredients	Formula (mg/tablet)			
	1	**a**	**b**	**ab**
Chlorpheniramine maleate	4.0	4.0	4.0	4.0
Sodium starch glycolate	4.0	8.0	4.0	8.0
Maltodextrin	4.0	4.0	8.0	8.0
Mg Stearate	1.0	1.0	1.0	1.0
Talc	2.0	2.0	2.0	2.0
Orange Flavor	2.0	2.0	2.0	2.0
Tartrazine	0.5	0.5	0.5	0.5
Mannitol	82.5	82.5	82.5	82.5

Table 2. Result flow properties of powder mixtures.

Flow Properties	Formula 1	Formula a	Formula b	Formula ab
Flow rate (g/s)	21.1 ± 0.289	33.4 ± 1.102	30.0 ± 0.520	31.6 ± 0.577
Angle of Repose (°)	41.60 ± 1.225	38.66 ± 0	31.86 ± 1.559	37.85 ± 1.396
Hausner Ratio	1.117 ± 0.004	1.222 ± 0.005	1.153 ± 0.001	1.249 ± 0.002
Carr's Index	10.447 ± 0.290	18.182 ± 0.354	13.307 ± 0.093	19.931 ± 0.120

Flow rate

A total of ± 100 g of powder mixture was placed into the flowability tester. The flow rate is calculated by dividing the weight of the powder by the time required for the powder to flow [8].

Angle of repose

A total of ± 100 g of powder mixture was placed into the funnel and dropped into the place provided under the funnel. The angle of repose testing is calculated from the tan arc between the height and radius of the powder [8].

Bulked density and tapped density

A total of ± 100 g of powder was poured gently into a graduated cylinder of 250 mL. The cylinder was then tapped 500 times. The volume of the powder that has been tapped is measured again as the final tapped density. Bulk density (ρb) and tapped density (ρt) were calculated [9].

$$\text{Bulk density (ρb)} = \frac{Weight\ of\ sample}{Bulked\ volume}$$

$$\text{tapped density (ρt)} = \frac{Weigh\ of\ sample}{Tapped\ volume}$$

Hausner ratio and Carr's index

The calculation of the hausner ratio value was done by comparing the bulked volume and the tapped volume, while to obtain the Carr's Index value, the calculation was done by comparing the difference between the bulked volume and the tapped volume and the bulked [9].

$$\text{Hausner Ratio} = \frac{Bulked\ volume}{Tapped\ volume}$$

$$\text{Carr's Index} = \frac{(Bulked\ volume - tapped\ volume)}{Bulked\ volume}\ x\ 100\%$$

Tablet organoleptic

Observations were made on the shape of the tablet and the presence of physical defects, colour, odour, and taste. Taste assessment is carried out to obtain qualitative data. Five healthy volunteers aged between 18-50 years were selected for the survey, with prior permission from the Health Research Ethics Commission. Each volunteer was asked to taste the tablet to assess the sweetness of the tablet preparation [10].

Tablet hardness

Hardness testing was carried out on 10 tablets, with replication three times for each formula. The harness requirement for FDT is that a tablet should dissolve in 1-3 kP [11].

Tablet friability

Tablet friability was measured using a friability tester by inserting 20 tablets that had gone through a dust removal process before weighed. Then the friability tester was set at 25 rpm for 4 minutes. At the end of the test, the tablets were dusted and reweighed. Each formulation was determined in triplicate. The percent loss in the weight of the tablet is the measure of friability and is expressed in percentage as the following equation [11].

$$\text{Friability Percent} = \frac{Loss\ in\ Weig}{Initial\ Weigh}\ x\ 100\%$$

Tablet disintegration

A total of 6 tablets were added to distilled water at 37±2°C. The longest tablet that disintegrated was measured. Each formulation was determined in triplicate [8, 11] . The time required to disintegrate the entire tablet is no more than 30 seconds.

Wetting time

A Whatman filter paper disc folded once diametrically was placed in a petri dish 10 cm in diameter containing 10 mL of red solution as an indicator. A tablet is placed on the middle of filter paper, and then the

time required for the water to wet the entire surface of the tablet is recorded [11],[13]. Each formulation was determined in triplicate.

Water absorption ratio

One tablet was weighed, and then placed on the tissue in a Petri dish with a diameter of 10 cm that had been wetted with red solution. The tablet was left until the red dye wetted all tablet surfaces. The wetted tablet was then weighed and the water absorption ratio was determined according to Equation [13].

$$\text{Absorption Ratio} = \frac{(tablet\ weights\ after\ wetting - tablet\ weigh\ before\ wetting)}{tablet\ weigh\ after\ wetting}\ 100\%$$

Statistical analysis

The physical properties of the tablets analyzed including hardness, friability, disintegration time, wetting time, and water absorption ratio. Analysis of Variance (ANOVA) is used to determine the significance of factors on the response while determining the effect of each factor is done by calculating the factor for each factor. The conditions for a preparation to be analyzed using ANOVA are that the preparation must be normally distributed and homogeneous with a confidence level of 95% and p value < 0.05. The normality test was carried out using the Shapiro-Wilk method, and the homogeneity test was carried out using the Levene test method. The optimum area is determined using Design Expert 13 by plotting the response to obtain a superimposed contour plot which is the optimum area for this research. Data resulting from verification of accuracy and precision methods are calculated to obtain SD and CV values.

Content uniformity

Content uniformity tests are carried out on selected formulas. Determined 10 tablets using an appropriate analytical method. Each tablet was weighed, crushed, and dissolved in 10.0 mL of 0.01 N HCl to obtain a 400 ppm CTM solution. Take 0.5 mL of the solution, adding 10.0 mL of solvent to obtain a CTM solution with a concentration of 20 ppm. The absorbance of the solution is then measured at 263 nm, and the concentration is calculated using the linear regression equation. The acceptance value is calculated based on the equation:

$$|M - \bar{x}| + Ks$$

M is the reference value, $\bar{x}$ is the average of each content, k is the acceptance constant, and s is the sample standard deviation [9].

Linearity testing

CTM standard series solutions were made with concentrations of 5, 10, 15, 20, 25, 30, and 35 ppm. The absorbance of each concentration is measured to obtain a linear regression between series concentration and absorbance [9].

Verification of accuracy and precision

Accuracy and precision were tested using the standard addition method. Prepare four 50 mL measuring flasks. Put 10.0 mL of sample solution into each volumetric flask. Add 10.0 mL, 15.0 mL, and 20.0 mL of stock solution respectively, to volumetric flasks 2, 3, and 4. Each volumetric flask is filled up to the mark with 0.01 N HCl solvent. There are three replications at each concentration. SD and CV are calculated to determine accuracy and precision [9].

▪ RESULTS AND DISCUSSION

The tablet manufacturing was done by the direct compression method. The powder needs to have characteristics in the form of good flow properties and compressibility. The flow properties of powder influence the tablet manufacturing process. Powder with good flow properties will fill the compression space in the machine constantly, so that the resulting tablets have the same weight uniformity [14]. Compressibility is the ability of powder to maintain a stable mass after being subjected to pressure, so this characteristic is related to the uniformity of the content of the tablets produced [15]. In this research, talcum is used as a lubricant to improve powder flowability. Based on Table 2, the results of powder flow rate testing ≥21.3 g/sec, angle of repose testing ≤41.99°, Hausner ratio, and Carr's index testing were ≤1.247 and ≤19.792. The

requirements for a good flow rate are more than 10 g/second, and a good angle of repose is in the range of 25^0 to 45^0 [8]. The angle of repose is an indirect method to determine the flow properties of a particle. The angle of repose describes the friction between particles, the higher the friction, the steeper the pile of particles will be, the angle will be smaller, and the flow properties will be better [16]. Based on USPC (2021), the Hausner ratio value is considered good, ranging between 1.112-1.18, and quite good if it is 1.19 to 1.25. The compressibility index is classified as good if it has a value of 11% to 15% and quite good if it has a value of 16% to 20%. Hausner ratio and compressibility index both describe the interactions between particles, which can be related to the flow properties of the particles. In powders with good flow properties, generally the interaction between particles is not significant, so the compressibility index and Hausner ratio values will be smaller [16],[17]. Thus, it can be stated that all formulas have flow and compressibility properties that meet the requirements for manufacturing with the direct compression method.

Table 3. Result of organoleptic testing chlorpheniramine maleate FDT.

Parameters	Formula 1	Formula a	Formula b	Formula ab
Color	Orange	Orange	Orange	Orange
Shape	Round, Flat	Round, Flat	Round, Flat	Round, Flat
Defect	some tablets experienced capping	some tablets experienced capping	-	-
Odor	Orange	Orange	Orange	Orange
Taste	Sweet	Sweet	Sweet	Sweet

As shown in Table 3, it can be concluded that the four formulas produce tablets with almost similar organoleptic properties. All four produce an orange colour, orange odor, flat round shape, and a sweet taste. The distinguishing characteristic is that in formulas 1 and a, a capping event occurred on several tablets. This is due to the lack of a binding agent in the preparation. Other factors that can have an influence are powder compressibility, which is not good enough, and compression speed, which is too high, causing air to be trapped between the powder particles. However, these factors are considered irrelevant in this case because formulas b and ab do not experience capping. even though they have similar conditions [18].

Table 4. Result of characteristic testing chlorpheniramine maleate FDT.

Characteristic	Formula 1	Formula a	Formula b	Formula ab
Hardness (kP)	1.045 ± 0.005	1.455 ± 0.025	2.252 ± 0.022	1.967 ± 0.008
Friability (%)	29.015 ± 0.058	31.044 ± 1.957	0.890 ± 0.048	13.154 ± 0.581
Disintegration Time (s)	20.277 ± 0.599	28.957 ± 1.039	26.543 ± 1.645	30.593 ± 2.002
Wetting Time(s)	27.697 ± 1.789	43.677 ± 2.329	36.137 ± 1.446	44.550 ± 0.435
Water Absorption Ratio (%)	129.445 ± 8.432	77.272 ± 3.547	73.523 ± 0.767	90.357 ± 4.502

Based on Table 4, it is known that of the four formulas, only formula b meets all the criteria that have been set. The four formulas meet the hardness criteria, namely 1-3 kP [11]. Meets the wetting time criteria, namely less than 180 seconds [19]. It also meets the criteria for a water absorption ratio, namely, not less than 70% [13]. However, both formulas 1, a, and ab did not meet the desired friability requirements, namely the loss of tablet weight of no more than 1%. This is because formulas 1 and a both involve high levels of SSG, so the resulting response is higher than formulas b and ab. Increasing the binder concentration results in a decrease in friability because the binder increases the bond between particles [20]. The ab formula is known to not meet the disintegration time requirements, this is because the composition of SSG is still too high, similar to research conducted by Farahiyah and Sulaiman [21], the disintegration mechanism of SSG is in the form of swelling if used in concentrations that are still quite high. This results in the tablet being less compact when under pressure, because of the large number of pores in the tablet. This causes the resulting pressure to not be strong enough to crush the tablet.

Effect of SSG and maltodextrin composition on chlorpheniramine maleate FDT characteristics

Table 5. Design factorial equation chlorpheniramine maleate FDT.

| Response	Design Factorial Equation
Hardness	$Y = -1{,}267 + 0{,}276X_A + 0{,}476X_B - 0{,}043X_AX_B$
Friability	$Y = 65{,}346 - 2{,}052X_A - 9{,}590X_B + 0{,}6397X_AX_B$
Disintegration Time	$Y = 0{,}701 + 3{,}328X_A + 2{,}724X_B - 0{,}289X_AX_B$
Wetting Time	$Y = 4{,}29 + 5{,}887X_A + 4{,}002X_B - 0{,}473X_AX_B$
Water Absorption Ratio	$Y = 306{,}547 - 30{,}295X_A - 31{,}232X_B + 4{,}313X_AX_B$

Table 5 shows the factorial design equation obtained based on the responses produced. Y is the violence response, X_A is the amount of SSG, X_B is the amount of maltodextrin, and X_AX_B is the composition of SSG and maltodextrin. This equation can be used to predict the response of the FDT produced based on the composition of SSG and maltodextrin used.

Table 6. Effect value of SSG, maltodextrin, and interaction.

| Response	SSG		Maltodextrin		Interaction	
	Effect	% Contribution	Effect	% Contribution	Effect	% Contribution
Hardness	0.0625	0.457	0.8595	85.471	-0.3475	12.982
Friability	7.147	8.379	-23.008	86.866	5.118	4.298
Disintegration Time	6.198	60.537	4.118	23.334	-2.482	8.008
Wetting Time	12.197	77.468	4.657	11.292	-3.784	7.454
Water Absorption Ratio	-17.669	15.371	-21.418	22.586	34.503	58.612

Table 6, illustrated that SSG, maltodextrin, and the interaction between the two have different influences and large contributions to the response produced. A positive value indicates that the factor influences increasing the FDT response, while a negative value indicates that the factor influences decreasing the response. The five responses produced a p-value <0.05, so it can be concluded that the two factors have a significant effect and there is an interaction between the two factors. The combination of SSG and Croscarmellose Sodium (CCS) has an effect on increasing tablet hardness when mixed with other hygroscopic excipients. The interaction between SSG and other hygroscopic excipients, in this case talc and magnesium stearate, can increase the compactibility and compressibility of the powder, resulting in increased hardness. Maltodextrin itself is a binder that works to increase the bond between powder particles, which causes an increase in tablet hardness [20]. The increase in disintegration time caused by both SSG and maltodextrin can be caused by the formation of a viscous layer that inhibits water penetration [11]. SSG, which is a superdisintegrant, is expected to shorten tablet disintegration time, but in this study, it gave the opposite response. This is caused by the disintegration mechanism of SSG itself, namely swelling, if used in concentrations that are still quite high, resulting in tablets that are less compact when under pressure, because of the large number of pores. in tablets. This causes the resulting pressure to not be strong enough to crush the tablet [21].

Figure 1 shows the interaction that occurs between the two factors. The interaction between the two factors is indicated by the shape of the lines, which are not parallel. The black line shown in letter (a) depicts low levels of maltodextrin, and the red line represents high levels of maltodextrin. Figure 1 shows (b) the black line depicts a low-level SSG and the red line depicts a high-level SSG.
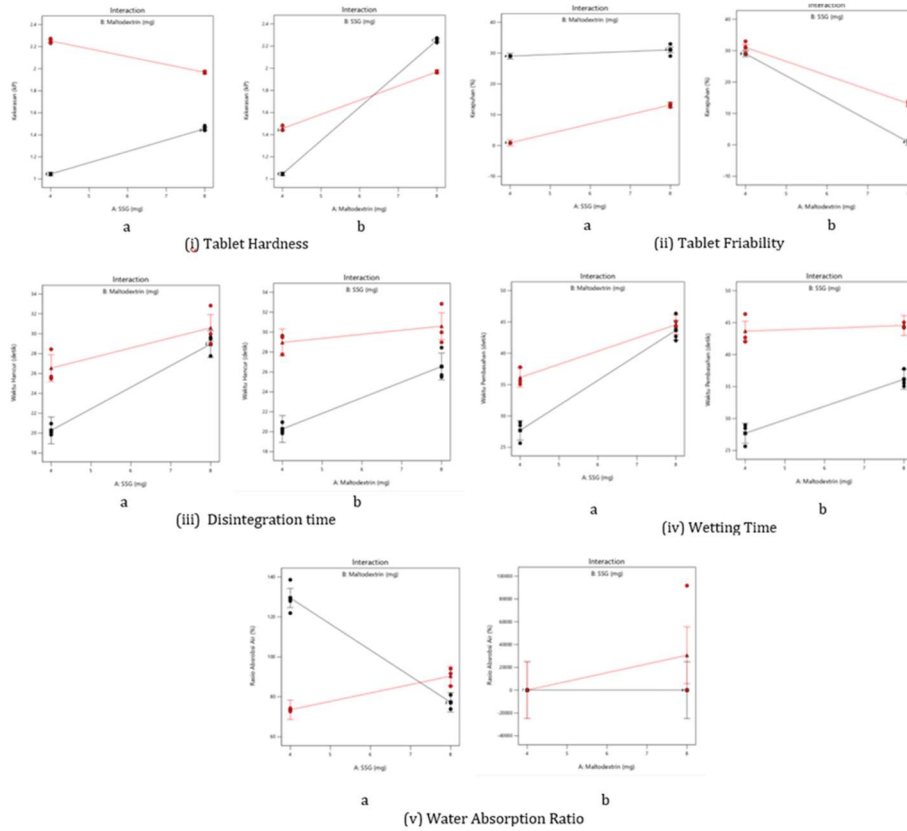
Figure 1. (a) Effects of SSG on high and low levels of maltodextrin (b) effects of maltodextrin on high and low levels of SSG to physical characteristics of chlorpheniramine maleate FDT.

Figure 2 shows a contour plot that depicts the red colour of the curve, indicating an increase in each response, and the bluer it is, indicating a decrease in the response to the preparation.
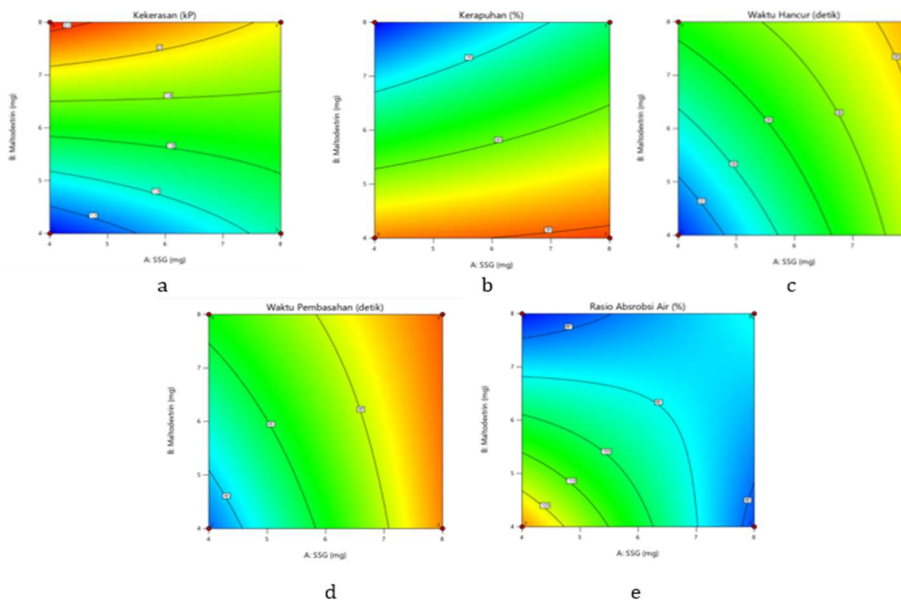
Figure 2. Contour plot of (a) hardness (b) friability (c) disintegrating time (d) wetting time (e) water absorption ratio response chlorpheniramine maleate FDT.

Determination of the optimum formula

A superimposed contour plot of SSG and maltodextrin was obtained based on the contour plot classification of hardness, friability, disintegration time, wetting time, and water absorption ratio, which is shown in Figure 3.
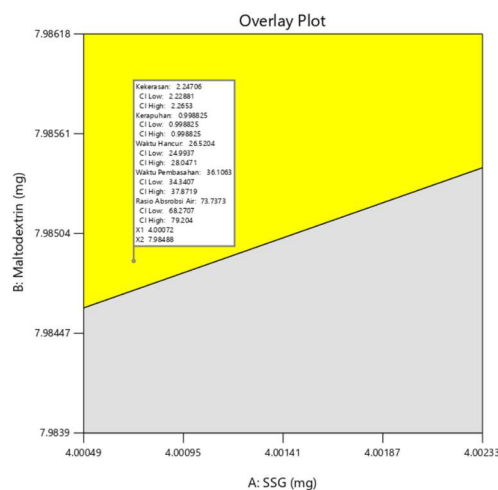

Figure 3. Superimposed contour plot of chlorpheniramine maleate FDT.

The yellow area shows the composition of SSG and maltodextrin, which produces optimal physical property responses, while the grey area shows the composition of SSG and maltodextrin, which cannot produce an optimal response.

A superimposed contour plot is determined in the hardness range 1-3 kP, maximum brittleness 1%, maximum disintegration time 30 seconds, maximum wetting time 180 seconds, and minimum water absorption ratio 70%. The optimum composition points for SSG and maltodextrin were found to be 4.00 mg and 7.98 mg respectively. This point is chosen based on the smallest composition that still falls within the specified optimum area, thereby increasing material efficiency.

Content uniformity testing

Method verification

The parameters set include linearity, accuracy, and precision. The linear regression equation $y = 0.0225x + 0.0236$ was obtained with a correlation coefficient (r) of 0.99865. According to the United States Pharmacopoeia Convention [22], the r value required to state good linearity is > 0.99. Accuracy and precision are determined using the standard addition method, the accuracy and precision requirements for analytes below 10 ppm, respectively are SBR <7.3% and an average recovery of 80-110% [23]. The research results showed that the SBR values were 2.762%, 1.433%, and 1.357% respectively, with a % recovery of 100.450%, 106.173% and 102.225%. From these data it can be concluded that the method used meets the requirements for linearity, accuracy and precision.

Determination of chlorpheniramine maleate FDT dosage form levels

The requirement for good content uniformity is that 10 tablets have an acceptance value of no more than 15.0 [9]. The k value for measuring 10 tablets is determined following the provisions in the Farmakope Indonesia, sixth edition, namely 2.4. From the average percent concentration of tablets, the M value can be determined and the acceptance value calculated. The acceptance value obtained was 5.039, so it can be concluded that the FDT CTM preparation produced had a uniform content.

- ▪ **CONCLUSION**

The Sodium starch glycolate (SSG) affects increasing hardness, increasing friability, extending disintegration time, extending wetting time, and reducing the water absorption ratio. Maltodextrin, has the effect of increasing hardness, reducing friability, extending disintegration time, extending wetting time, and reducing the water absorption ratio. The interaction of SSG and maltodextrin has the effect of reducing hardness, increasing friability, shortening disintegration time, shortening wetting time, and increasing the water absorption ratio.

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