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Characterization of modified sorghum starch and its use as a film-forming polymer in orally dissolving film formulations with glycerol as a plasticizer

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ABSTRACT: Film-forming polymers and plasticizers are components of orally dissolving film (ODF) compositions that have the greatest influence on the physical properties of the film preparations. Modification of sorghum starch produces maltodextrin (MDX)-sorghum which can be used as a film-forming polymer, and glycerol can be used as a plasticizer in ODF preparations. This study aims to determine the optimal concentrations of MDX-sorghum and glycerol to produce ODF compositions using the central composite design (CCD) in response surface methodology (RSM). Hydrolysis of sorghum starch yielded MDX-sorghum, characterized by yield value, dextrose equivalent (DE) value, solubility, swelling power and FTIR analysis. The CCD included a concentration range of 2-6% and 3-10% for MDX-sorghum and glycerol, respectively, as parameters in the optimization process, so 14 experimental designs were obtained. The test response was evaluated using tensile strength, elongation and disintegration time tests. The modification of sorghum starch yields a light brown MDX-sorghum powder with desirable properties. Optimization of MDX-sorghum and glycerol concentrations yielded an optimal formulation with a tensile value of 1.50 mPa with an error percentage of 0.33%, elongation of 104.26% with an error percentage of 0.25%, and disintegration time of 82.95 seconds with an error percentage of 0.06%. By modifying sorghum starch into MDX-sorghum, the starch's ability to dissolve and swell can be improved, allowing it to be used as a film-forming polymer. The optimal MDX-Sorghum and glycerol concentrations for the production of ODF are 3.56% and 10.00 %, respectively.

KEYWORDS: Sorghum strach, modified, film-forming, glycerol, response surface methodology.

1. INTRODUCTION

Sorghum starch is a film-forming polymer with hydrophilic properties used in the manufacture of orally dissolving film (ODF) preparations [1]. Sorghum starch is a natural biopolymer that is easily accessible and contains 72–75% carbohydrates, 20–30% amylose, and 70–80% amylopectin, which can be used as film-forming components [2,3]. However, natural sorghum starch has several disadvantages: it is sticky, hard, brittle, not transparent, and not resistant to acid treatment. In a study by Putri et al. (2018), using only sorghum starch resulted in a less elastic film preparation. This problem can be overcome by modifying sorghum starch through a partial hydrolysis process so that its characteristics resemble those of maltodextrin (MDX) [4]. MDX is obtained from starch that has been enzymatically modified by partial hydrolysis. As a result, MDX has a dextrose equivalent (DE) value of less than 20. Moreover, MDX is a film-forming polymer that has good solubility and adhesive characteristics, allowing it to produce elastic films [5,6].

The film-forming polymer influences the film preparation's elasticity; plasticizers can also increase film's elasticity [7]. Glycerol is one of the plasticizers that can be used in the manufacture of ODF preparations. Glycerol is a plasticizer that is easily soluble in water (hydrophilic), has a low molecular weight and thus helps to reduce intermolecular tensions along the polymer chain, and provides the advantages of increasing the viscosity of the solution, reducing brittleness, and increasing the strength of ODF preparations [8]. Glycerol, as a plasticizer, produced edible films with improved characteristics compared with sorbitol and polyethylene glycol [9]. A research conducted by Walfathiyyah et al. (2017) showed that adding of glycerol resulted in a

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more elastic edible film [10]. The optimal concentrations of glycerol and MDX-sorghum can be analyzed using the response surface methodology (RSM).

RSM can be used to design several formulations with varying concentrations of MDX-sorghum and glycerol. The RSM can reduce the number of materials used because it does not require a trial formulation stage, which would require considerable research [11]. Furthermore, this method can describe the interaction among variables toward the response [11,12]. Several models can be used in RSM. The experimental design in this study used the central composite design (CCD) model. CCD is a fractional factorial design often used in RSM as it can speed up several experimental designs [13]. The concentration of MDX-sorghum which functions as a film-forming agent and glycerol which functions as a plasticizer were the independent factors, while the dependent variables (response) were tensile strength, elongation and disintegration time. MDX-sorghum and glycerol as components in the manufacture of films are expected to produce films with characteristics that meet the requirements so that they can be used as alternative pharmaceutical preparations containing cetirizine HCl. Cetirizine HCl is available in tablet dosage forms. However, the disadvantage of tablet preparations is that pediatric and geriatric patients and patients with throat disorders have difficulty swallowing tablets, resulting in decreased patient compliance. Therefore, alternative preparations are required to make it easier for these patients to consume cetirizine, such as oral dissolving film (ODF) preparations that dissolve rapidly in the mouth [14,15]. Hence, it is necessary to optimize the concentrations of MDX-sorghum and glycerol to produce ODF preparation with optimal physical properties. The research findings can serve as a reference for developing natural excipients.

2. RESULTS AND DISCUSSION

2.1. Characteristics of MDX-Sorghum

The characteristics of sorghum starch and MDX-sorghum are shown in Table 1. Based on the results, the DE value of MDX-sorghum met the requirements (i.e., < 20). Low DE maltodextrin (< 20) had better elasticity and viscosity than high DE maltodextrin [16]. In each sugar chain undergoing hydrolysis, there was one reducing sugar group; as the number of simple sugar groups increased, the number of reducing sugar groups and the value of DE also increased. In solubility and swelling power studies, MDX-sorghum demonstrated more solubility and swelling ability than sorghum starch. This was due to the hydrolysis reaction performed by the amylase enzyme on sorghum starch by breaking the glycosidic bond in starch molecules into simple sugars, such as glucose and dextrin, so that the two parameters increased [5,6].

Table 1. Characteristics of sorghum starch and modified sorghum starch

No	Inspection	Sorghum Starch	MDX-Sorghum
1	Organoleptic:		
	Form	Powder	Powder
	Texture	Fine/smooth	Fine/smooth
	Aroma	Typical Sorghum	Brown sugar
	Flavour	Slightly Sweet	Slightly Sweet
	Colour	Light brown	Dark brown
2	Dextrose Equivalent	0.84	6.22
3	Swelling Power	2.44	2.87
4	Solubility	12.52%	52.9%
5	Yield Value	-	86.71%

Sorghum starch and modified sorghum starch were analyzed by evaluating the spectrum's shape, namely the specific peaks indicating the type of functional group ina starch compound. The FTIR analysis results are shown in Figure 1 and 2. The O–H group's peak is between 3,400 and 2,100 cm^{-1}. At approximately 3,270.7 cm^{-1}, the yield of sorghum starch groups was measured, whereas the O-H functional group was identified at the peak of modified sorghum starch at 3,287.0 cm^{-1}. The C-H functional group was discovered at the peak of 2,924.1 cm^{-1} within the range of 3,850.0–2,924.1 cm^{-1}, with no variation in peak positions between samples. With a wavelength of 1,149.9 cm^{-1} and a peak transition of 1,148.0 cm^{-1}, the C-O-C functional group was found in sorghum starch, showing a change in the modified starch. This test is intended to identify transfer results between functional groups in two spectra, allowing for the observation of transmission differences between O-H and C-O-C functional groups. The amylase enzyme breaks the -1,4 glycosidic link in the polysaccharide chain for starch to be turned into MDX [17].

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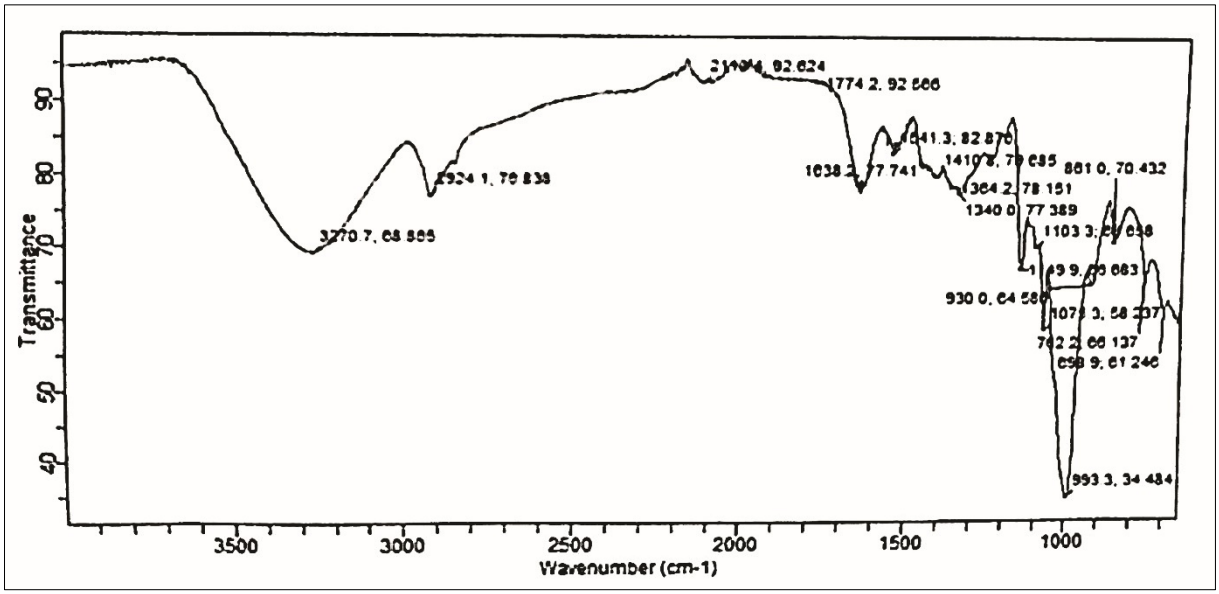

Figure 1. FTIR Spectrum of Sorghum Starch

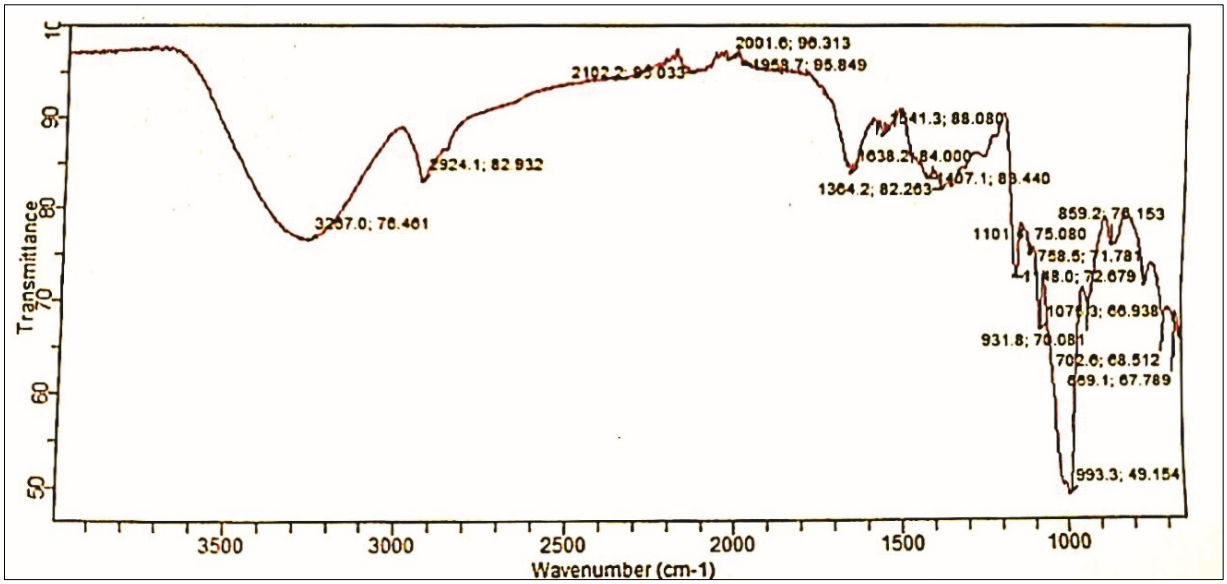

Figure 2. FTIR Spectrum of MDX-Sorghum

2.2. Evaluation of ODF Preparations

Table 2 presents the results of the evaluation of ODF preparations. Based on the evaluation, all ODF formulations meet the requirements of a 'good' film. The film preparation was considered good if it had a tensile strength value of 1.02 – 10.20 mPa [18], elongation > 70% [19], and disintegration time < 3 minutes [20].

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Table 2. Evaluation of ODF Preparations

Run	Factor		Response		
	A: MDX-Sorghum Concentration (%)	B: Glycerol Concentration (%)	Y_1: Tensile Strength (mPa)	Y_2: Elongation (%)	Y_3: Disintegration Time (sec)
1.	4.00	6.50	1.98	86.26	152
2.	4.00	3.00	2.47	66.74	181
3.	4.00	10.00	1.52	101.68	75
4.	4.00	6.50	1.92	89.44	155
5.	5.41	8.97	1.32	103.96	85
6.	4.00	6.50	1.67	91.94	160
7.	2.59	8.97	1.48	97.72	112
8.	4.00	6.50	1.95	86.58	158
9.	6.00	6.50	1.61	99.16	90
10.	4.00	6.50	1.98	93.18	150
11.	4.00	6.50	1.91	84.84	159
12.	2.59	4.03	1.87	61.41	191
13.	2.00	6.50	2.05	72.41	176
14.	5.41	4.03	1.58	78.56	166

2.3. Data Analysis Using RSM

The combination of MDX-Sorghum as a film-forming agent and glycerol as a plasticizer affects the tensile strength, elongation, and disintegration time, as illustrated in Figure 3. The color on the graph represents the tensile strength (a), elongation (b), and disintegration time (c). The color positioned bottom has the lowest response value, while the above color has the highest response value. The number of color changes along the curve indicates the influence of the concentrations film-forming agent (A) and plasticizer (B). The combination of factors (A and B) affects the response related to the number of colors on the curve [14,18]. According to the observed results, the disintegration time is the response most affected by the concentration of the factors.

2.3.1. Tensile strength

The results of the tensile strength data analysis indicated that the factors influenced the tensile strength. In the 14 formulations, tensile strength results ranged from of 1.32 to 2.47 mPa. The results met the requirements for good tensile strength, namely 1.02–10.20 mPa [9,18]. Based on the analysis results (Table 3), the suggested analytical model was a linear model based on the sum of the squares of the tensile strength response model sequence. The linear model with an R-squared value of 0.56 showed that the polymer concentration and the plasticizer concentration influenced the tensile strength responses. The adjusted R-squared value of 0.56 served as a generalization of the population's R-Squared due to the existence of the population estimation element [21]. The model equation for the tensile strength response was Y_1 = +1.81 - 0.13*A - 0.25*B based on the results in Table 3. The equation shows that the coefficients of the polymer concentration (A) and the plasticizer concentration (B) were -0.13 and -0.25, respectively. It indicates that a decrease in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1). The tensile strength decreases as the polymer and/or plasticizer content increases. This is because MDX-sorghum has a low molecular weight, making the polymer network less intense and decreasing the film's mechanical properties [22]..The plasticizer can reduce the strong intermolecular attraction in the polysaccharide chain of MDX-sorghum and promote hydrogen formation between the plasticizer and polysaccharide molecule, thereby weakening the hydrogen bonds in the polymer and decreasing the tensile strength of the film [23].

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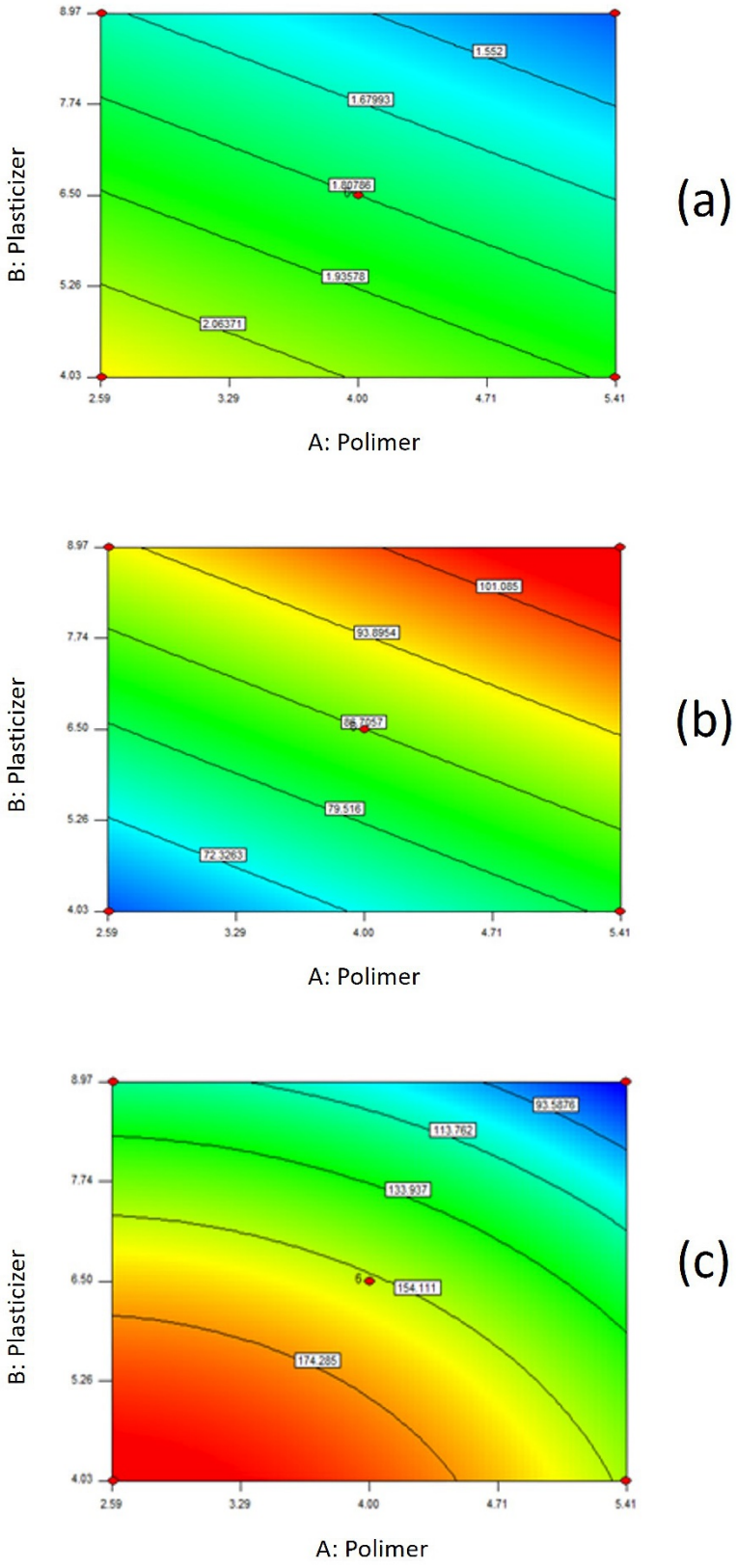

Figure 3. Graph showing the effect of film-forming polymer (MDX-Sorghum) concentration and plasticizer (glycerol) concentration on tensile strength value (a), elongation (b), and disintegration time (c)

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2.3.2. Elongation

Elongation data indicated the influence of factors on the elongation results. In the 14 formulations, the elongation results were between 61.41–103.96%. Consequently, a linear model based on the sum of squares of the elongation response was suggested based on the analysis results (Table 3). In addition, the findings of the lack-of-fit test indicated that a linear model should be applied to the elongation response in order to produce the correct model. This linear model fitted the elongation response with a p value (prob>F) of 0.2747, indicating its validity [11,13]. Y_2 = +86.71 +7.67*A +13.90*B was the model equation for the elongation response depending on the data in Table 3. Based on the equation, coefficients of the the polymer concentration (A) and the plasticizer concentration (B) were +7.67 and +13.90, respectively. It indicates that an increase in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1). The higher the concentration of polymer and/or plasticizer, the more likely the elongation is to increase. This occurs because the glycerol molecules in the polymer matrix disrupt the polymer structure through hydrogen bonds and transform it into an irregular flexible structure, a process that can be considered as restructuring (rearrangement) of the polymer matrix, with increased resistance towards received pressures which in turn increase the stretchability (elongation) of the film [23]. This is also because maltodextrin cannot create a strong network with other polymers that make ODF [22].

Table 3. Analysis of ODF Cetirizin HCl Tensile Strength, Elongation, and Disintegration Time Using CCD

Factors		Y_1 Tensile Strength (mPa)	Y_2 Elongation (%)	Y_3 Disintegration Time (sec)
A (MDX-Sorghum Concentration (%))	Coefficient	-0.13	7.67	-21.75
	ρ-value	0.1031	0.0002**	0.0003**
B (Glycerol Concentration (%))	Coefficient	-0.25	13.90	-38.78
	ρ-value	0.0070**	0.0001**	0.0001**
A. B	Coefficient	-	-	-0.50
	ρ-value	-	-	0.9238
A^2	Coefficient	-	-	-9.37
	ρ-value	-	-	0.0364*
B^2	Coefficient	-	-	-11.87
	ρ-value	-	-	0.0130*
Analytical model		Linear	Linear	Quadratic
Intercept		1.81	86.71	155.68
Degree of freedom		2	2	5
Sum of squares		0.64	2012.01	17342.43
Mean of squares		0.32	1006.00	3468.49
F-value		7.04	62.85	33.80
ρ-value		0.0108	0.0001	0.0001
R-Squared		0.5613	0.9195	0.9548

* ρ-value < 0.05
** ρ-value < 0.01

2.3.3. Disintegration time

Based on results of the disintegration time test, the film could disintegrate within 75–191 seconds. According to the results of the study described in Table 3, the suggested analytical model was a quadratic model based on the sum of the squares of the sequence of the disintegration time response models. The findings of the analysis of variance using the suggested quadratic model confirmed this. Furthermore, the p value (prob>F) of 0.0001 was smaller than 0.05, indicating a significant model to determine the interaction of responses to variables in the disintegration time response [11,13]. Based on Table 3, the model equations for the disintegration time response were: Y_3 = +155.68-21.75*A-38.78*B-0.50*A*B-9.37*A^2-11.87*B^2. Based on the equation, the polymer concentration (A) and the plasticizer concentration (B) were -21.75 and -38.78,

respectively. It indicates that a decrease in polymer and/or plasticizer concentration results an increase in the disintegration time response (Y3). The higher the concentrations of polymer and/or plasticizer, the faster the disintegration. This occurs due to the increase in polymer concentration. MDX, which has a high solubility in water and aids water penetration into the film structure, provides a shorter disintegration time [24,25]. Therefore, when the concentrations of polymer and plasticizer are high, the disintegration time is short. This result is in line with a study by Sri et al. (2018), which found that increasing the amount of MDX made the film disintegrate more rapidly [26]. The plasticizer can increase the intermolecular gap of the film, and the enhanced intermolecular gap can allow water to migrate and accelerate the film's disintegration [9].

2.4. ODF Preparation Optimal Formulation

Based on our experiments, the recommended model to observe the effect of the use of MDX-sorghum and glycerol on the tensile strength and elongation responses was a linear model. In contrast, the suggested model for the disintegration time response was a quadratic model. The optimal ODF formulation was verified by reproducing the formulation by the RSM recommendations, and testing was performed for tensile strength, elongation, and disintegration time. From the results listed in Table 4, the recommended optimal concentrations of MDX-sorghum and glycerol were 3.56% and 10%, respectively, with a predicted tensile strength value of 1.495 mPa, percent elongation of 104%, and disintegration time of 83 seconds. The prediction results were validated by producing an ODF with the optimal formulation, which was then evaluated.

Table 4. Results of Optimal Oral Dissolving Film (ODF) Formulation on Response

No	Polymer (%)	Plasticizer (%)	Tensile Strength (mPa)	Elongation (%)	Disintegration Time (sec)	Desirability
1.	3.56	10.00	1.495	104.0	83	0.807
2.	3.55	10.00	1.497	103.9	83	0.806
3.	3.53	10.00	1.499	103.8	83	0.804

The validation of the RSM prediction results is presented in Table 5. The results indicated no significant difference (percentage error < 0,05%) between the results obtained and the RSM predictions. Therefore, the ODF preparation met the requirements for good film-forming characteristics. The literature shows that using polymers and plasticizers affects the characteristics of ODF. A high plasticizer concentration would result in low tensile strength, short disintegration time, and a high elongation value [25].

Table 5. Optimal ODF Evaluation Results

No	Response	RSM Prediction	Observation Results	Percentage Error (%)
1	Tensile Strength (mPa)	1.495	1.50	0.33
2	Elongation (%)	104	104.26	0.25
3	Disintegration Time (second)	83	82.95	0.06

3. CONCLUSION

The modified sorghum starch resulted in MDX-sorghum with enhanced solubility and swelling power. At a concentration of 2-6%, MDX-sorghum can be used as a film-forming polymer with the required tensile strength, elongation (%), and disintegration time. Based on the CCD analysis, the optimal concentrations of MDX-sorghum and glycerol were 3.56% and 10.00% respectively, with a tensile strength response of 1.50 mPa with an error percentage of 0.33%, 104,26% elongation with an error percentage of 0.25%, and a disintegration time of 82,95 seconds with an error percentage of 0.06%. On the foundation of the obtained data, it can be stated that sorghum starch modification can increase the use of sorghum as a pharmaceutical excipient.

4. MATERIALS AND METHODS

4.1. MDX-Sorghum Production

In the production of MDX-sorghum, the sorghum was modified by dissolving sorghum starch (Timurasa, Indonesia) using distilled water to a concentration of 24% (w/v). The pH of the solution was adjusted to 6 using HCl (Merck, Germany) and NaOH (Merck, Germany). Then, 100 ppm anhydrous $CaCl_2$ (Merck, Germany) and 0.5% (v/v) amylase enzymes (Hench Biotechnology, China) were added. The solution was stirred at 87^{o}C for 90 minutes. After the stirring was complete, the inactivation process began by adding

HCl until the pH reached to 4. The solution was then cooled to 60ºC and neutralized using 0.1 M NaOH until the pH reached to 6. The solution was then placed into an oven at 50ºC in a thin layer. After drying, the powder was mashed with a blender, and sieved through a 100-mesh sieve. The MDX-sorghum characterization was then performed [2,5].

4.2. MDX-Sorghum Characterization

4.2.1. Yield value

The resulting MDX-sorghum was weighed entirely, and the yield value was calculated using the following equation [27,28]:

$$Yield\ (\%) = \frac{MDX - sorghum\ weight\ obtained}{weight\ of\ sorghum\ starch\ used}\ x\ 100$$

4.2.2. Dextrose equivalent (DE) value

In order to calculate the DE value, firstly, the Fehling Factor value was calculated. 2.5 g of glucose was dissolved in distilled and the volume was made up1,000 mL with distilled water. Then 15 mL of the solution was removed and added 5 mL each of Fehling's solutions A and B. The mixture was boiled. While boiling, it was titrated with glucose solution until it turned reddish-brown. The amount of titrant required was recorded, and the Fehling Factor was calculated using the following equation [5,28]:

$$FF = \frac{titrant\ volume\ mL\ x\ glucose\ weight\ (g)}{1{,}000}$$

The DE value was then calculated by preparing 10 g/200 mL solution of MDX-sorghum and taking it into the burette. Then, 5 mL each of Fehling's solutions A and B, as well as 15 mL of glucose solution, were added to 50 mL of distilled water. The solution was heated and titrated with the solution of MDX-sorghum until a reddish brown colour was obtained. The required titrant was then recorded, and the DE value was calculated using the following equation [5,28]:

$$DE = FF\ x\ \frac{100}{starch\ concentration\ \left(\frac{g}{mL}\right) x\ titrant\ volume\ (mL)}$$

4.2.3. Solubility

A total of 0.5 g of the sample was weighted (b) then dissolved in 10 mL of distilled water and vortexed for 30 seconds. The solution was then centrifuged for 15 minutes at 3000 rpm. After that, 5 mL of the supernatant was separated and dried in an oven at 105°Cfor 5 hours. The product was then weighed and the result was recorded as weight (a). The solubility (%) of the sample was then calculated using the following equation [27,29]:

$$Solubility\ (\%) = \frac{a}{b}\ x\ 2\ x\ 100$$

4.2.4. Swelling power

A total of 0.1 g of MDX-sorghum (b) was mixed with 10 mL of distilled water and heated at 60°C with steady stirring for 30 minutes in a water bath. The samples were centrifuged at 1,600 rpm for 15 minutes. The precipitate was weighted (a) and the swelling strength was calculated using the following equation [27]:

$$Swelling\ Power = \frac{a}{b}$$

4.2.5. Fourier transform Infra-Red (FTIR) analysis

Two grams of MDX-sorghum were milled and weighed. The sample was added to 200 g of KBr and mixed until homogeneous. It was then placed into a pellet mold and analyzed for the MDX-sorghum functional group using FTIR (Agilent cary 630). The sample was scanned 64 times at resolution 2 cm^{-1} above the spectral range of 4,000–400 cm^{-1} [30,31].

4.3. Production of ODF Cetirizine HCl

The CCD method in RSM was used to optimize the MDX-sorghum and glycerol concentrations. Because of the lack of fit tests, the CCD technique required five to six repetitions of the center point to estimate the pure error. Hence, Table 2 offers six formulas with the same concentrations of MDX-sorghum and glycerol. The ODF was produced through the solvent casting method, employing the composition listed in Table 6.

Table 6. ODF cetirizine HCl composition based on CCD

Run	Batch	Composition						
		Cetirizine HCl (mg)	MDX-Sorghum* (%)	Glycerol* (%)	Sucrose (%)	Citric Acid (%)	HPMC (%)	Distilled Water ad (mL)
1.	F1	1.50	4.00	6.50	4	4	4	100
2.	F2	1.50	4.00	3.00	4	4	4	100
3.	F3	1.50	4.00	10.00	4	4	4	100
4.	F4	1.50	4.00	6.50	4	4	4	100
5.	F5	1.50	5.41	8.97	4	4	4	100
6.	F6	1.50	4.00	6.50	4	4	4	100
7.	F7	1.50	2.59	8.97	4	4	4	100
8.	F8	1.50	4.00	6.50	4	4	4	100
9.	F9	1.50	6.00	6.50	4	4	4	100
10.	F10	1.50	4.00	6.50	4	4	4	100
11.	F11	1.50	4.00	6.50	4	4	4	100
12.	F12	1.50	2.59	4.03	4	4	4	100
13.	F13	1.50	2.00	6.50	4	4	4	100
14.	F14	1.50	5.41	4.03	4	4	4	100

*CCD-RSM Concentration Design Results

First, citric acid (4 g) and sucrose (4 g) were dissolved using distilled water (mass A). MDX-sorghum was then added in hot water and was stirred until it dispersed (mass B). In hot water, 4 g of Hydroxypropyl Methyl Cellulose (HPMC) (Luxchem, Indonesia) was mixed and dispersed (mass C). Mass C was mixed with mass B and glycerol until it was homogeneous. Then, mass A and cetirizine HCl (Kimia Farma, Indonesia) were added and mixed until it was homogeneous. The distilled water was added until the volume of the mixture reached to 100 mL and it was agitated until homogeneous. The mixture was poured and placed on the mold, before heating at 50°C for 24 hours. The obtained film was then removed from the mold and sliced to a 2 × 2 cm^2 size [3].

4.4. Evaluation of ODF Preparation and Cetirizine HCl

4.4.1. Tensile strength and elongation test

Tensile strength and elongation tests were performed using the universal testing machine located at the Centre for Advanced Materials Science and Technology (Pusat Sains dan Teknologi Bahan Maju-PSTBM), Batan, Serpong, South Tangerang

.4.4.2. Disintegration time test

A film was placed in a petri dish containing 2 mL of distilled water. The time required for the film to completely disintegrate was recorded as the disintegration time [32].

4.5. Data Analysis

Response data in the form of tensile strength, elongation and disintegration time were entered into the CCD-RSM (Design Expert 7.1.5, trial version) response column and were analyzed to obtain the optimal concentration of MDX-sorghum and glycerol for producing ODF preparations that best met the requirements. The level and limits of the response variables in data analysis using CCD are within range, where the requirements for a good ODF include tensile strength values between 1.02 - 10.2 mPa [15], elongation percentage more than 70 % [16] , and disintegration time less than 3 minutes. The optimum MDX-sorghum and glycerol concentration was determined from the formula with the highest desirability value. [16,18].

4.6. Production and Evaluation of the Optimal ODF Formulation

The optimal formulation obtained from CCD-RSM analysis was produced and evaluated. The results of the tensile strength, elongation and disintegration time tests were then compared with the predicted RSM data.

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