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   - Revisions and Amends
   - Revised version with highlights
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6. Paper accepted (28 April 2023)
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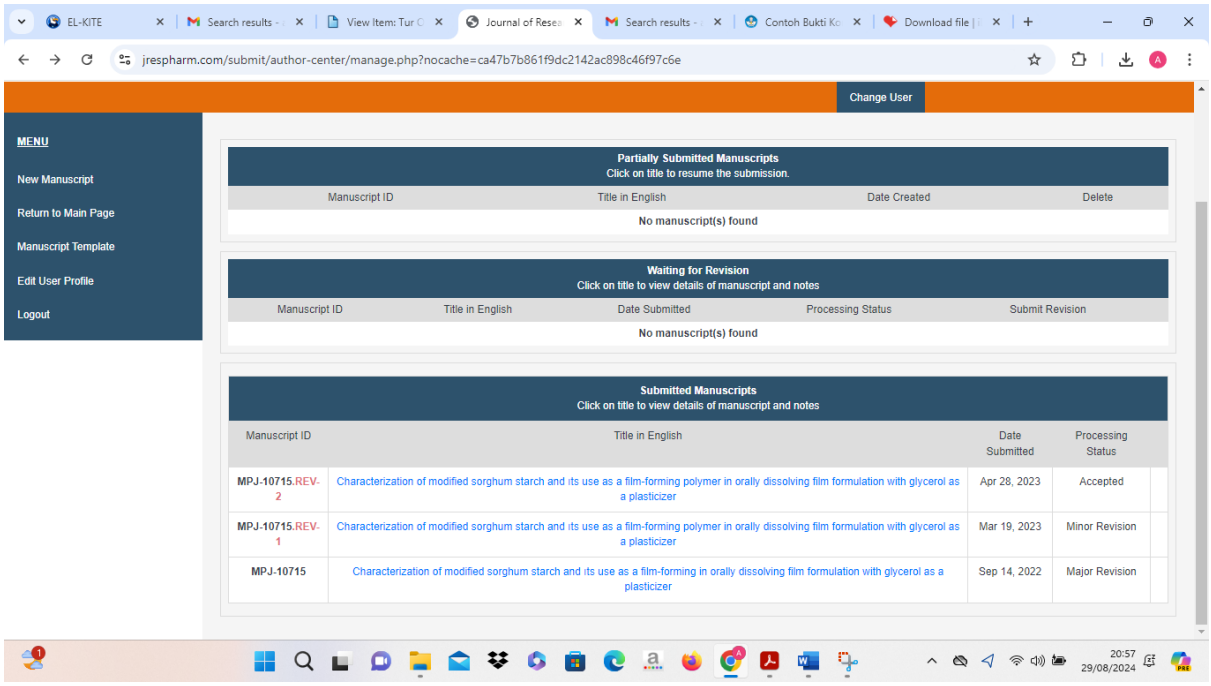

Submitted to the journal “Journal of Research in Pharmacy” (14 September 2022)

Journal of Research in Pharmacy : Confirmation for your submission External Inbox ×

Journal of Research in Pharmacy <editor@marmarapharmj.com> Sep 14, 2022, 3:08 PM

to me

Journal of Research in Pharmacy
An international open-access journal of pharmacy and pharmaceutical sciences
Formerly published as Marmara Pharmaceutical Journal

JRP
ISSN : 2630-6344

Dear Anisa Amalia,

Thank you for submitting your manuscript entitled "Characterization of modified sorghum starch and its use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer" to
Journal of Research in Pharmacy . Your manuscript will first be evaluated by the editors and if it meets the Journal's standards, will be forwarded to referees for scientific review. You will be able to follow the stage of your manuscript in the review process through the author center to which you will have access with your user name and password. You can use the author center for revisions and new submissions.

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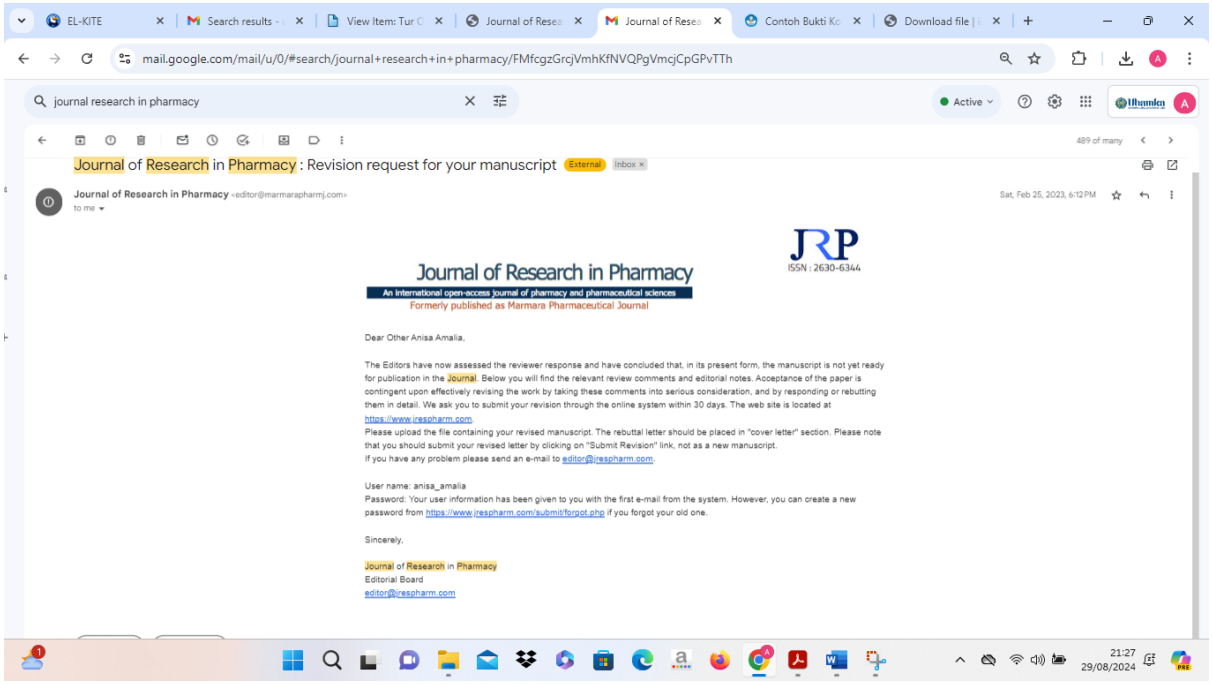
First revision: Accepted with major revision (25 Februari 2023)



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Sat, Feb 25, 2023, 6:12 PM

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Dear Other Anisa Amalia,

The Editors have now assessed the reviewer response and have concluded that, in its present form, the manuscript is not yet ready for publication in the Journal. Below you will find the relevant review comments and editorial notes. Acceptance of the paper is contingent upon effectively revising the work by taking these comments into serious consideration, and by responding or rebutting them in detail. We ask you to submit your revision through the online system within 30 days. The web site is located at https://www.jrespharm.com.
Please upload the file containing your revised manuscript. The rebuttal letter should be placed in "cover letter" section. Please note that you should submit your revised letter by clicking on "Submit Revision" link, not as a new manuscript.
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User name: anisa_amalia
Password: Your user information has been given to you with the first e-mail from the system. However, you can create a new password from https://www.jrespharm.com/submit/forgot.php if you forgot your old one.

Sincerely,

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Change User

Suggestions

1.Reviewer Comments
Work is presented well. Few changes are suggested as given in track changes.

2.Reviewer Comments
The manuscript entitled "Characterization of modified sorghum starch and its use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer" was about an oral dissolving film formulation that contains a modified sorghum starch. Authors modified sorghum starch to eliminate its undesired properties (such as stickiness and brittleness) and used it as a pharmaceutical excipient. There are serious inconsistencies between Tables 4-5, the abstract, and the conclusion sections in the manuscript. These inconsistencies cause confusion and must be corrected. In addition, the quality of the figures should be improved. Particularly, it is hard to read the numbers in Figures 1 and 2. There are also several misspelled words and grammar errors. In conclusion, I believe the manuscript may only be suitable for publication after a revision. Details are specified in the word document.

3.Reviewer Comments
My comments and corrections have been made on the attached file.

Reviewer 1

Comment File Show Comment File (https://www.jrespharm.com/submit/uploads/rev_com/MPJ-10715-14503-rev-file-10715-mpj-10715-3-modified-sorghum-starch-jrp-review-comments.docx)

Reviewer 2

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Reviewer 3

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Manuscript Information

Manuscript ID: **MPJ-10715**

Title in English: Characterization of modified sorghum starch and ıts use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer

Small Title in English: No information entered

Authors: Anisa Amalia[1], Nining Nining[1], Muhammad Dandi[2]

Institutions: [1]Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Department of Pharmaceutics, East Jakarta/DKI Jakarta, Indonesia
[2]Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Department of Pharmacy, East Jakarta/DKI Jakarta, Indonesia

Keywords in English: Sorghum strach ; modified ; film-forming ; glycerol ; response surface methodology

Manuscript Type: Research article

Processing Status: Major Revision

Abstract in English

Film-forming polymers and plasticizers are the components of Orally dissolving film (ODF) compositions that have the most 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 for producing ODF compositio 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 design included a 2-6% and 3-10% concentration range for MDX-sorghum and glycerol, respectively, as parameters in the optimization process. The test response was evaluated using tensile strength, elongation, and disintegration time tests, so 14 experimental designs were obtained. 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 formula with a tensile value of 1.81 MPa with an error percentage of 0.33%, an elongation of 104% with an error percentage of 0.33%, and a disintegration time of 82.95 seconds with an error percentage of 0.06%. By modifying sorghum starch to make MDX-sorghum, the starch's properties can be enhanced and used as a film-forming. The optimal MDX-Sorghum and glycerol concentrations for the production of ODF are 3.56 % and 10 %, respectively.

Manuscript Files

File Name	File Size	Date Created	Category	Description
MPJ-10715-2-cover-letter-jrp.pdf (../pdf-files/out/10715-MPJ-10715-2-cover-letter-jrp.pdf)	14 KB	Sep 14, 2022	Cover letter	None
MPJ-10715-3-modified-sorghum-starch-jrp-template.pdf (../pdf-files/out/10715-MPJ-10715-3-modified-sorghum-starch-jrp-template.pdf)	1305 KB	Sep 14, 2022	Main Document	None
MPJ-10715-1-jrp-checklist.pdf (../pdf-files/in/10715-MPJ-10715-1-jrp-checklist.pdf)	241 KB	Sep 14, 2022	Author Checklist Form	None
MPJ-10715-4-modified-sorghum-starch-jrp-template.pdf (../pdf-files/out/10715-MPJ-10715-4-modified-sorghum-starch-jrp-template.pdf)	0 KB	Sep 14, 2022	Main Document	None
MPJ-10715-1-jrp-copyright-form-integrated.pdf (../pdf-files/out/10715-MPJ-10715-1-jrp-copyright-form-integrated.pdf)	85 KB	Sep 14, 2022	Copyright Transfer Form	None
MPJ-10715-6-figure-1.jpg (../pdf-files/in/10715-MPJ-10715-6-figure-1.jpg)	98 KB	Sep 14, 2022	Figure	None
MPJ-10715-5-figure-1.jpg (../pdf-files/in/10715-MPJ-10715-5-figure-1.jpg)	0 KB	Sep 14, 2022	Figure	None

MPJ-10715-9-figure-2.jpg (../pdf-files/in/10715-MPJ-10715-9-figure-2.jpg)	89 KB	Sep 14, 2022	Figure	None
MPJ-10715-9-figure-3.jpg (../pdf-files/in/10715-MPJ-10715-9-figure-3.jpg)	103 KB	Sep 14, 2022	Figure	None

Score Sheet

1. Reviewer

Does the content and value of the work justify publication in Marmara Pharmaceutical Journal ?	Yes
Does the title of the manuscript reflect the contents of the study ?	Yes
Are the keywords sufficient and appropriate ?	Yes
Is the summary concise and informative?	Yes
Is the text divided appropriately according to the article type ?	Yes
Is the language adequate?	Yes
Are the nomenclature and scientific terminology correct?	Yes
Are the references complete and recent?	Yes
Are the figures tables and graphics necessary ?	Yes
Are the figures tables and graphics clear ?	Yes

Is the introduction part	sufficiently developed
Are the experimental procedures sound?	Yes
Is the results and discussion part	sufficiently developed
Is conclusion sufficient and correlated with the results ?	Yes
Is the information about the approval of ETHICAL COMMISSION presented ?	Not applicable

2. Reviewer

Does the content and value of the work justify publication in Marmara Pharmaceutical Journal ?	After revision
Does the title of the manuscript reflect the contents of the study ?	Yes
Are the keywords sufficient and appropriate ?	Yes
Is the summary concise and informative?	Yes
Is the text divided appropriately according to the article type ?	Yes
Is the language adequate?	Yes

Are the nomenclature and scientific terminology correct?	Yes
Are the references complete and recent?	Yes
Are the figures tables and graphics necessary ?	Yes
Are the figures tables and graphics clear ?	No
Is the introduction part	sufficiently developed
Are the experimental procedures sound?	Yes
Is the results and discussion part	sufficiently developed
Is conclusion sufficient and correlated with the results ?	No
Is the information about the approval of ETHICAL COMMISSION presented ?	Not applicable

3. Reviewer

Does the content and value of the work justify publication in Marmara Pharmaceutical Journal ?	Yes
Does the title of the manuscript reflect the contents of the study ?	Yes
Are the keywords sufficient and	Yes

appropriate ?	
Is the summary concise and informative?	Yes
Is the text divided appropriately according to the article type ?	Yes
Is the language adequate?	No
Are the nomenclature and scientific terminology correct?	Yes
Are the references complete and recent?	No
Are the figures tables and graphics necessary ?	Yes
Are the figures tables and graphics clear ?	No
Is the introduction part	sufficiently developed
Are the experimental procedures sound?	Yes
Is the results and discussion part	sufficiently developed
Is conclusion sufficient and correlated with the results ?	No
Is the information about the approval of ETHICAL COMMISSION presented ?	Not applicable

RESPONSE TO REVIEWERS
OF THE JOURNAL OF RESEARCH IN PHARMACY

MANUSCRIPT ID: MPJ-10715

Reviewer: 1

Comments to the Author

Work is presented well. Few changes are suggested as given in track changes.

Response:

Thank you for your correction suggestion. We apologized for the mistakes in our writing. We have enhanced the writing and added the reasons for selecting cetirizine HCl and the advantages of establishing the ODF formula as an alternative method of delivering cetirizine HCl. The bibliography has been rewritten and a DOI hyperlink has been included.

Reviewer: 2

The manuscript entitled "Characterization of modified sorghum starch and its use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer" was about an oral dissolving film formulation that contains a modified sorghum starch. Authors modified sorghum starch to eliminate its undesired properties (such as stickiness and brittleness) and used it as a pharmaceutical excipient. There are serious inconsistencies between Tables 4-5, the abstract, and the conclusion sections in the manuscript. These inconsistencies cause confusion and must be corrected. In addition, the quality of the figures should be improved. Particularly, it is hard to read the numbers in Figures 1 and 2. There are also several misspelled words and grammar errors. In conclusion, I believe the manuscript may only be suitable for publication after a revision. Details are specified in the word document.

Response:

Thank you for your improvement suggestion. We apologise for the mistakes in our writing. We have reviewed and updated the results stated in the abstract, conclusions, and tables 4 and 5. The resolution of figures 1-3 has been enhanced. We have corrected and rechecked for writing and grammar issues utilising a language editing service.

Reviewer: 3

My comments and corrections have been made on the attached file

Response:

Please accept our apologies for our writing errors and thank you for your improvement recommendations. The required amount of material has been incorporated into the methodology. The reason there are four identical formulas is because, according to the CCD model, it takes five to six repetitions of concentration to estimate the test error, and we have included this to the methodology section (4.3). The writing of the library has been enhanced, and a DOI hyperlink has been included. The image resolution has been enhanced.

Journal of Research in Pharmacy

Research Article

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

Anisa AMALIA[1*], Nining NINING[1], Muhammad DANDI[2]

[1] Department of Pharmaceutics, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia.
[2] Department of Pharmacy, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia
* Corresponding Author. E-mail: anisa.amalia@uhamka.ac.id (A.A.); Tel. +62-85691775915.

Received: 0 Month 201X / Revised: 0 Month 201X / Accepted: 0 Month 201X

ABSTRACT: Film-forming polymers and plasticizers are ~~the~~ components of ~~O~~orally dissolving film (ODF) compositions that have the ~~most~~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 ~~for~~to produce~~ing~~ 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 ~~design~~ included a concentration range of 2-6% and 3-10% ~~concentration range~~ 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, ~~so 14 experimental designs were obtained~~. 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 1.5081 MPa with an error percentage of 0.33%, ~~an~~ elongation of 104.26% with an error percentage of 0.2533%, and ~~a~~ 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. ~~By modifying sorghum starch to make MDX-sorghum, the starch's properties can be enhanced and used as a film-forming~~ The optimal MDX-Sorghum and glycerol concentrations for the production of ODF are ~~3.56~~3.56 % and 10.0010 %, 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~~ing~~ of orally dissolving film (ODF) preparations ~~([1]) [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:~~there are several drawbacks to natural sorghum starch:~~ it is sticky, hard, brittle, not transparent, and not resistant to acid treatment. In a study by Putri et al. ~~[([3])]~~, using ~~only~~single 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 has good film-forming, solubility, and adhesive characteristics, allowing it to produce elastic films [5,6].

The film-forming polymer influence~~d~~ 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 ~~to help bring down the~~ intermolecular tensions along the polymer chain, and provides~~has~~ the

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How to cite this article: Amalia A, Nining N, Dandi M. Characterization of modified sorghum starch and its use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer. J Res Pharm. 2019; 23(6): 1-XX.

ISSN: 2630-6344

https://doi.org/10.12991/jrp.2019.00

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 Rresearch conducted by Walfathiyyah et al. (2017) showed that adding of glycerol resulted in a 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 ~~the value of~~ tensile strength, ~~percentage~~ 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 ~~for the~~ 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.~~Therefore, it is necessary to optimize the concentrations of MDX-sorghum and glycerol to obtain an ODF preparations with the best physical properties so that it can be used as a reference in the development of natural excipients in the pharmaceutical field.~~

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~~three parameters increased [5,6].

Sorghum starch and modified sorghum starch were analyzed by evaluating the spectrum's shape, namely the specific peaks indicating the type of functional group in~~by~~ a starch compound. The FTIR analysis results ~~using FTIR~~ 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]).~~The peak for the O-H group was in the range of 3,400–2,400 cm^{-1}. The results of the sorghum starch group were around 3,270.7 cm^{-1}, while the O-H functional group was obtained at a modified sorghum starch peak of 3,287.0 cm^{-1}, and the C-H functional group was obtained at the peak of 2,924.1 cm^{-1} in the range of 3,850.0–2,850.0 cm^{-1}, indicating no change in peak between the two samples. However, the C-O-C functional group obtained 1,149.9 cm^{-1} of sorghum starch and a peak shift of 1,148.0 cm^{-1}, which indicated a change in the modified starch. This treatment aimed to determine the results of the transfer between the functional groups on the two spectra, whereby the difference between the transmittance in the O-H and C-O-H functional groups could be observed.~~

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~~This was due to the breakdown of 1,4 glycosidic bonds by the amylase enzyme on the inside of the polysaccharide chain so that the starch could be modified into~~ MDX [14].

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 Mppa ([18]) ~~[15]~~, elongation > 70% ([19]) ~~[16]~~, and disintegration time < 3 minutes ([20]) ~~[17]~~.

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 ~~percentage~~ (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)~~ing concentrations~~. 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 ~~concentration~~.

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]) ~~[9]~~. 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 ~~diversity of~~ tensile strength responses. The adjusted R-squared value of 0.56~~13~~ served as a generalization of the population's R-Squared due to the existence of the population estimation element ([21]). ~~[11]~~. 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 ~~value~~ concentration (A) ~~was -0.13~~ and the plasticizer concentration ~~value~~ (B) ~~was~~ were -0.13 and -0.25, respectively. It indicate~~sing~~ that a decrease in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1) ~~an increase in the tensile strength response (Y_1) that was influenced by a decrease in the polymer concentration and a decrease in plasticizer concentration~~. 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 higher the concentrations of polymer and/or plasticizer, the lower the tensile strength. This is because,~~ t~~T~~he 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]). ~~[19]~~.

2.3.2. Elongation

Elongation ~~percent~~ 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 order~~ 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-p value (Pprob>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 ~~value~~ concentration (A) ~~was +7.67,~~ and the plasticizer ~~value~~ concentration (B) ~~was~~were +7.67 and +13.90, respectively. It indicate~~sing~~ that an increase in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1)~~an increase in elongation response (Y_2) influenced by an increase in polymer concentration and plasticizer concentration~~. 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

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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 ~~(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]). ~~[19].~~

2.3.4. 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: $Y_3 = +155.68-21.75*A-38.78*B-0.50*A*B-9.37*A^2-11.87*B^2$.

~~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, a quadratic model, confirmed this. Furthermore, the Pp 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. 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 ~~value~~ concentration (A) ~~was -21.75,~~ and the plasticizer ~~value~~ concentration (B) ~~was~~were -21.75 and -38.78, respectively. It indicates~~ing~~ that a decrease in polymer and/or plasticizer concentration results an increase in the disintegration time response (Y3) ~~that was influenced by a decrease in polymer concentration and a decrease in plasticizer concentration~~. The higher the concentrations of polymer and/or plasticizer, the faster the disintegration ~~time~~. This occurs due to the increase in polymer concentration. ~~The shorter disintegration time is caused by~~ MDX, which has a high solubility in water, ~~which~~and aids water penetration into the film structure, provides a shorter disintegration time ([24,25]) ~~[24]~~. Therefore, when the concentrations of polymer and plasticizer are high, the disintegration time is ~~low~~short. This result is in line with a study by Sri et al. (2018), which found that increasing the amount of MDX ~~would make~~ made the film disintegrate more rapidly ([26]) ~~[21]~~. 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.

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]) ~~[22]~~.

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~~4.00~~% and 10.00~~6.50~~% respectively, with a tensile strength response of 1.50~~81~~ MPa, 104.26~~86.71~~% elongation, and a disintegration time~~period~~ of 82.95~~156~~ seconds. On the foundation

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of the obtained data, it can be stated that sorghum starch modification can increase the use of sorghum's use 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 aquadest to a concentration of 24% (w/v), with tThe pH of the solution was adjusted to 6 using HCl (Merck, Germany) and NaOH (Merck, Germany) to pH 6. 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°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 a temperature of 60°C and neutralized using 0.1 M NaOH until the pH reached to pH 6. The solution was then placed into an oven at 50°C in a tin in a thin layer. After drying, the powder was removed, mashed with a blender, and sieved through a 100-mesh sieve.. The MDX-sorghum characterization was then performed [2,5].

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4.2. MDX-Sorghum Characterizsation

4.2.1. Yield value

The resulting MDX-sorghum was weighed entirely, and the yield value was calculated using the following Eequation ([27,28]) [23,24]:

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

4.2.2. Dextrose Equivalent (DE) Value

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In order to calculate the DE value, firstly, the Fehling Factor value was calculated. The DE value started by finding the Fehling factor value by dissolving 2.5 g of glucose was dissolved inwith distilled and the volume was made upwater up to 1,000 mL with distilled water., Tthen removing 15 mL of the solution was removed and addeding 5 mL each of Fehling's solutions A and B. The mixture was boiled, and While boiling, it was titrated in a boiling state with glucose solution until it turnedbecame reddish-brown. The amount of titrant required was recorded, and the Fehling fFactor was calculated using the following Eequation ([5,28]); [5,24]:

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

The DE value was then calculated by preparing a 10 g/200 mL solution of MDX-sorghum and inserting 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 athe solution of MDX-sorghum until a reddish brown colour was obtained. The required titrant iswas then recorded, and the DE value iswas calculated using the following Eequation ([5,28]) [5,24]:

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

4.2.3. Solubility

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A total of 0.5 g of the sample was weighted (b) then dissolved in 10 mL of distilled water and before being vortexed for 30 seconds. The solution was then centrifuged for 15 minutes at 3000 rpm. In additionAfter that, 5 mL of the solution supernatant was separated and driedevaporated in an oven at 105-°C, until for 5 hours. The product wasis then weighed and the result wasis recorded as weight (a). The solubility (%) of the sample wasis then calculated using the following Eequation ([27,29]) [23,25]:

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

4.2.4. Swelling Power

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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 ~~utilizing~~ Equation ([27]) ~~[23,25]~~:

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

4.2.5. Infra-Red Fourier Transform (FTIR) Analysis

MDX-sorghum was milled~~ground~~ and 2 g of the sample was 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 wave number region~~spectral range of 4,000–400 cm^{-1} ([30,31]). ~~[26,27]~~.

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. ODF was produced using the solvent casting method ~~(see Table 6 for composition)~~. First, citric acid (4 g) and sucrose (4 g) were dissolved using distilled water ~~to become~~ (mass A). MDX-sorghum was then added~~dispersed~~ in hot water and was stirred until it dispersed~~expanded, forming~~ (mass B). In hot water, 4 g of Hydroxypropyl Methyl Cellulose (HPMC) (Luxchem, Indonesia) was mixed and dispersed ~~and mixed~~ (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 ~~remaining~~ 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 ~~being~~ heatinged ~~for 24 hours~~ at 50°C for 24 hours. The ~~created~~ obtained film ~~is~~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 ~~percentage~~ 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 ~~is~~was recorded as the disintegration time ([32]) ~~[28]~~.

4.5. Data Analysis

Response data in the form of tensile strength ~~test results~~, elongation, and disintegration times 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]) ~~[17]~~.

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, ~~percentage~~ elongation, and disintegration time tests were then compared with the predicted RSM data.

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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	72.58%	86.71%

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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

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Table 3. Analysis of ODF Cetirizin HCl Tensile Strength, ~~Percent~~ 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		Liniear	Liniear	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

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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

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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

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Table 6. ODF cetirizine HCl composition based on CCD

Run	Batch	Composition						
		Cetirizine HCl (mg)	MDX-Sorghum* (%)	Glycerol* (%)	Sucrose (%)	Citric Acid (%)	HPMC (%)	Distilled WaterAq ~~uadest~~ ad (mL)
1.	F1	1,500	4.00	6.50	4	4	4	100
2.	F2	1,500	4.00	3.00	4	4	4	100
3.	F3	1,500	4.00	10.00	4	4	4	100
4.	F4	1,500	4.00	6.50	4	4	4	100
5.	F5	1,500	5.41	8.97	4	4	4	100
6.	F6	1,500	4.00	6.50	4	4	4	100
7.	F7	1,500	2.59	8.97	4	4	4	100
8.	F8	1,500	4.00	6.50	4	4	4	100
9.	F9	1,500	6.00	6.50	4	4	4	100
10.	F10	1,500	4.00	6.50	4	4	4	100
11.	F11	1,500	4.00	6.50	4	4	4	100
12.	F12	1,500	2.59	4.03	4	4	4	100
13.	F13	1,500	2.00	6.50	4	4	4	100
14.	F14	1,500	5.41	4.03	4	4	4	100

*CCD-RSM Concentration Design Results

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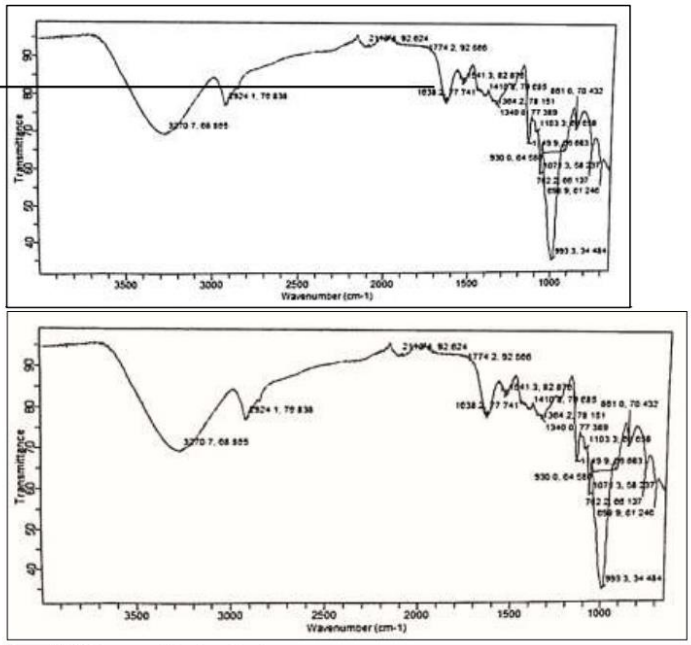

Figure 1. FTIR Spectrum of Sorghum Starch

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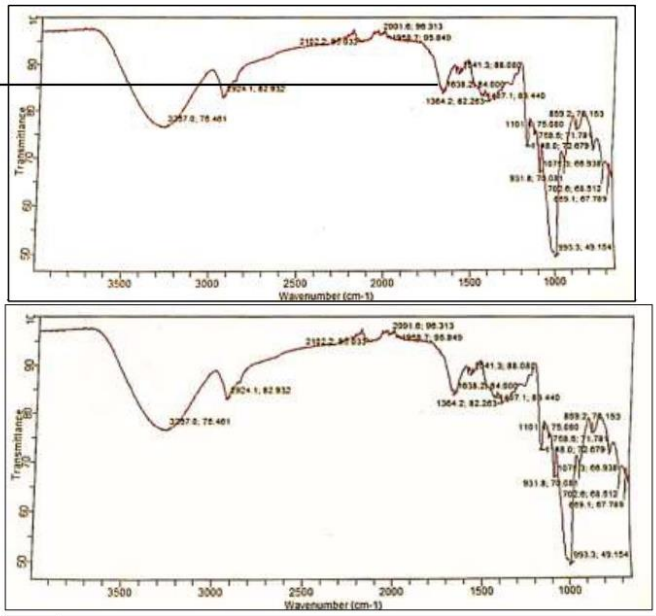

Figure 2. FTIR Spectrum of MDX-Sorghum

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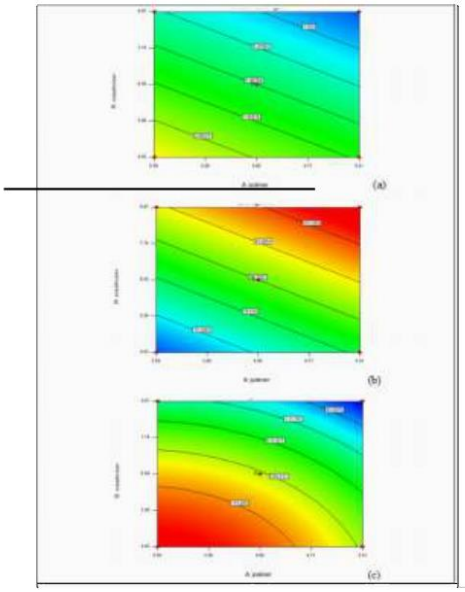

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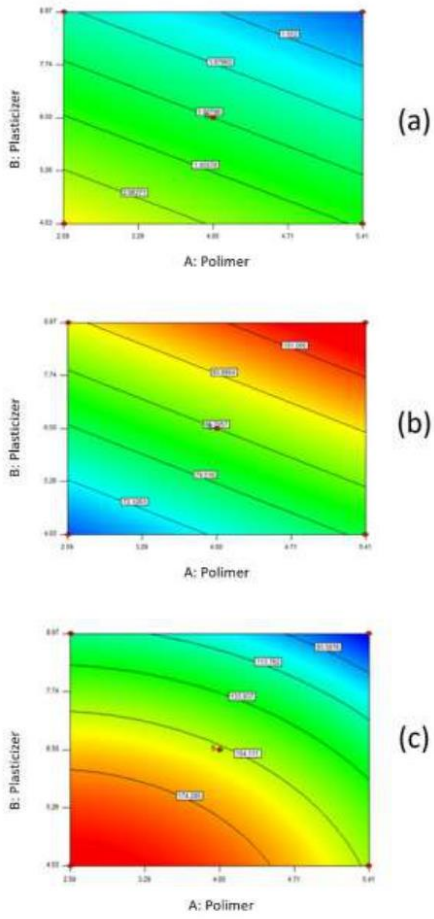

Figure 3. Graph showing the effect of film-forming polymer (MDX-Sorghum) concentration and plasticizer (glycerol) concentration on tensile strength value (a), ~~percentage of~~ elongation (b), and disintegration time (c)

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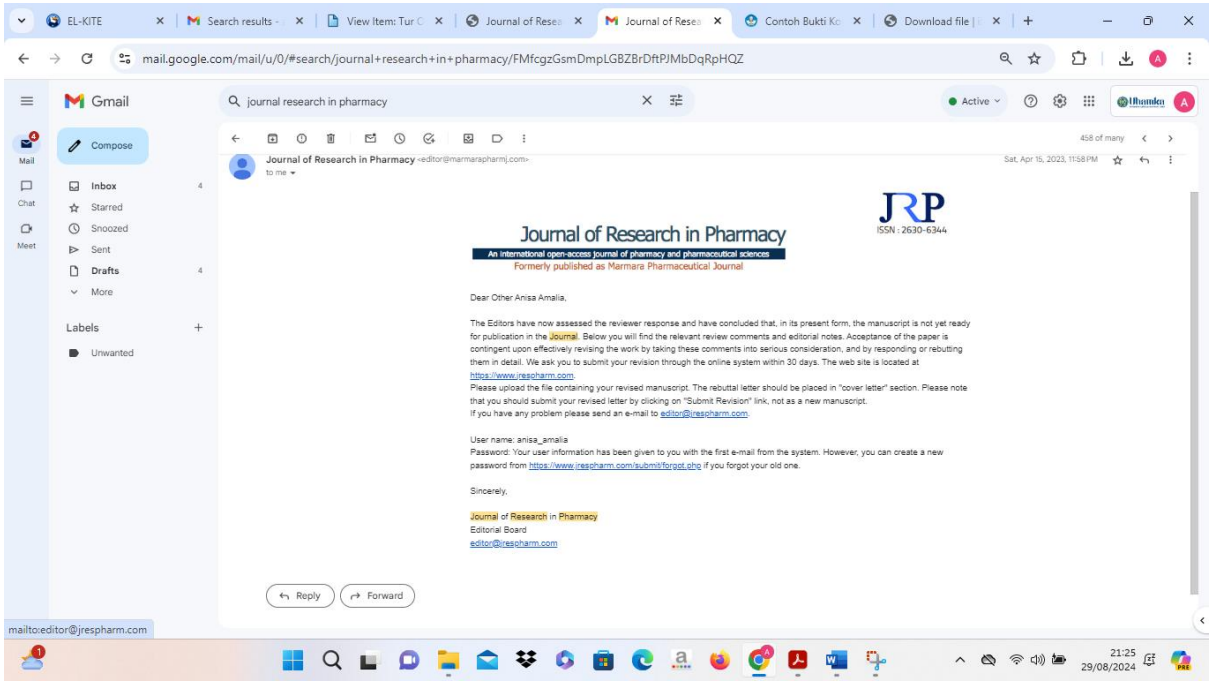
Second revision: Minor revision (15 April 2023)



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Thank you for your all corrections. I have just fixed a few punctuation marks.
I think it is appropriate to publish it as it is. Please find the attached file.

2.Reviewer Comments
The revised manuscript is much better than the original one. One typo I can see after the revision is some decimal points written with a comma (,) instead of a period (.) in the conclusion section. I have no further queries or comments for the authors. I believe the manuscript is now suitable for publication after the correction stated above.

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Manuscript Information

Manuscript ID: **MPJ-10715.REV-1**

Title in English: Characterization of modified sorghum starch and ıts use as a film-forming polymer in orally dissolving film formulation with glycerol as a plasticizer

Small Title in English: No information entered

Authors: Anisa Amalia[1], Nining Nining[1], Muhammad Dandi[2]

Institutions: [1]Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Department of Pharmaceutics, East Jakarta/DKI Jakarta, Indonesia
[2]Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Department of Pharmacy, East Jakarta/DKI Jakarta, Indonesia

Keywords in English: Sorghum strach ; modified ; film-forming ; glycerol ; response surface methodology

Manuscript Type: Research article

Processing Status: Minor Revision

Manuscript Files

File Name	File Size	Date Created	Category	Description
MPJ-10715-2-cover-letter-jrp.pdf (../pdf-files/out/12582-MPJ-10715-2-cover-letter-jrp.pdf)	14 KB	Sep 14, 2022	Cover letter	None

MPJ-10715-3-modified-sorghum-starch-jrp-template.pdf (../pdf-files/out/12582-MPJ-10715-3-modified-sorghum-starch-jrp-template.pdf)	1305 KB	Sep 14, 2022	Main Document	None
MPJ-10715-1-jrp-checklist.pdf (../pdf-files/in/12582-MPJ-10715-1-jrp-checklist.pdf)	241 KB	Sep 14, 2022	Author Checklist Form	None
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Is the results and discussion part	sufficiently developed
Is conclusion sufficient and correlated with the results ?	Yes
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Are the experimental procedures sound?	Yes

Is the results and discussion part	sufficiently developed
Is conclusion sufficient and correlated with the results ?	Yes
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Second revision submitted (28 April 2023)

RESPONSE TO REVIEWERS
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MANUSCRIPT ID: MPJ-10715

Reviewer: 1

Comments to the Author

Thank you for your all corrections. I have just fixed a few punctuation marks.

I think it is appropriate to publish it as it is. Please find the attached file.

Response:

Thanks for the guidance and suggestions. We rewrote the paragraph because we were unable to include citations in its sentences.

Reviewer: 2

The revised manuscript is much better than the original one. One typo I can see after the revision is some decimal points written with a comma (,) instead of a period (.) in the conclusion section. I have no further queries or comments for the authors. I believe the manuscript is now suitable for publication after the correction stated above.

Response:

Thanks for the guidance and suggestions. We have fixed the typing mistake

Journal of Research in Pharmacy

Research Article

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

Anisa AMALIA[1*], Nining NINING[1], Muhammad DANDI[2]

[1] Department of Pharmaceutics, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia.
[2] Department of Pharmacy, Faculty of Pharmacy and Science, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia
* Corresponding Author. E-mail: anisa.amalia@uhamka.ac.id (A.A.); Tel. +62-85691775915.

Received: 0 Month 201X / Revised: 0 Month 201X / Accepted: 0 Month 201X

ABSTRACT: Film-forming polymers and plasticizers are ~~the~~ components of ~~O~~orally dissolving film (ODF) compositions that have the ~~most~~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 ~~for~~to produce~~ing~~ 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 ~~design~~ included a concentration range of 2-6% and 3-10% ~~concentration range~~ for MDX-sorghum and glycerol, respectively, as parameters in the optimization process. So that 14 experimental designs were obtained. The test response was evaluated using tensile strength, elongation, and disintegration time tests, ~~so 14 experimental designs were obtained~~. 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 1.5081 MPa with an error percentage of 0.33%, ~~an~~elongation of 104.26% with an error percentage of 0.2533%, and a 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. ~~By modifying sorghum starch to make MDX-sorghum, the starch's properties can be enhanced and used as a film-forming~~ The optimal MDX-sSorghum and glycerol concentrations for the production of ODF are ~~3.56~~3.56 % and 10.0010 %, 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~~ing~~ of orally dissolving film (ODF) preparations ~~([1]) [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:~~there are several drawbacks to natural sorghum starch:~~ it is sticky, hard, brittle, not transparent, and not resistant to acid treatment. In a study by Putri et al. ~~[([3])]~~, using ~~only~~sing~~le~~ 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 has good film-forming~~, solubility~~, and adhesion~~ve~~ properties as well as good solubility~~characteristics~~, allowing it to produce elastic films [5,6].

The film-forming polymer influence~~s~~d 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 ~~to help bring down the~~ intermolecular tensions along the polymer chain, and provides~~has~~ the

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Commented [GŞ3]: Compare with the all values written in conclusion section, there are differences.

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Commented [GŞ5]: What is "film-forming solubility" ?

How to cite this article: Amalia A, Nining N, Dandi M. Characterization of modified sorghum starch and its use as a film-forming in orally dissolving film formulation with glycerol as a plasticizer. J Res Pharm. 2019; 23(6): 1-XX.

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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 Rresearch conducted by Walfathiyyah et al. (2017) showed that adding of glycerol resulted in a 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 the value of tensile strength, percentage 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 for the 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.

~~Therefore, it is necessary to optimize the concentrations of MDX-sorghum and glycerol to obtain an ODF preparations with the best physical properties so that it can be used as a reference in the development of natural excipients in the pharmaceutical field.~~

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 twothree parameters increased [5,6].

Sorghum starch and modified sorghum starch were analyzed by evaluating the spectrum's shape, namely the specific peaks indicating the type of functional group inby a starch compound. The FTIR analysis results using FTIR 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]).~~The peak for the O-H group was in the range of 3,400–2,400 cm^{-1}. The results of the sorghum starch group were around 3,270.7 cm^{-1}, while the O-H functional group was obtained at a modified sorghum starch peak of 3,287.0 cm^{-1}, and the C-H functional group was obtained at the peak of 2,924.1 cm^{-1} in the range of 3,850.0–2,850.0 cm^{-1}, indicating no change in peak between the two samples. However, the C-O-C functional group obtained 1,149.9 cm^{-1} of sorghum starch and a peak shift of 1,148.0 cm^{-1}, which indicated a change in the modified starch. This treatment aimed to determine the results of the transfer between the functional groups on the two spectra,

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~~whereby the difference between the transmittance in the O-H and C-O-H functional groups could be observed. This was due to the breakdown of -1,4 glycosidic bonds by the amylase enzyme on the inside of the polysaccharide chain so that the starch could be modified into~~ MDX [14].

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 Mppa ([18]) ~~[15]~~, elongation > 70% ([19]) ~~[16]~~, and disintegration time < 3 minutes ([20]) ~~[17]~~.

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 ~~percentage~~ (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) ~~ing concentrations~~. 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 ~~concentration.~~

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]) ~~[9]~~. 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 ~~diversity of~~ tensile strength responses. The adjusted R-squared value of 0.56~~13~~ served as a generalization of the population's R-Squared due to the existence of the population estimation element ([21]). ~~[11]~~. 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 ~~value~~ concentration (A) ~~was -0.13~~ and the plasticizer concentration ~~value~~ (B) ~~was~~ were -0.13 and -0.25, respectively. It indicate~~sing~~ that a decrease in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1) ~~an increase in the tensile strength response (Y_1) that was influenced by a decrease in the polymer concentration and a decrease in plasticizer concentration~~. 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 higher the concentrations of polymer and/or plasticizer, the lower the tensile strength. This is because,~~ [T]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]). ~~[19]~~.

2.3.2. Elongation

Elongation ~~percent~~ 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 order~~ 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-p~~ value (Pprob>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 ~~value~~ concentration (A) ~~was +7.67,~~ and the plasticizer ~~value~~ concentration (B) ~~was~~were +7.67 and +13.90, respectively. It indicate~~sing~~ that an increase in polymer and/or plasticizer concentration results in an increase in tensile strength response (Y_1) ~~an increase in elongation response (Y_2) influenced by an increase in polymer concentration and plasticizer concentration~~. The higher the concentration of polymer and/or plasticizer, the more likely the elongation is to increase. [This

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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 ~~(resistance)~~ towards received pressures which in turn increase the stretchability (elongation) of the film ([23]). This is also because maltodextrin can not create a strong network with other polymers that make ODF ([22]). ~~[19]~~.

2.3.4. 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: $Y_3 = +155.68-21.75*A-38.78*B-0.50*A*B-9.37*A^2-11.87*B^2$.

~~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, a quadratic model, confirmed this. Furthermore, the Pp 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. 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 ~~value~~ concentration (A) ~~was -21.75~~, and the plasticizer ~~value~~ concentration (B) ~~was~~were -21.75 and -38.78, respectively. It indicates~~ing~~ that a decrease in polymer and/or plasticizer concentration results an increase in the disintegration time response (Y3) ~~that was influenced by a decrease in polymer concentration and a decrease in plasticizer concentration~~. The higher the concentrations of polymer and/or plasticizer, the faster the disintegration ~~time~~. This occurs due to the increase in polymer concentration. ~~The shorter disintegration time is caused by~~ MDX, which has a high solubility in water, ~~which~~and aids water penetration into the film structure, provides a shorter disintegration time ([24,25]) ~~[24]~~. Therefore, when the concentrations of polymer and plasticizer are high, the disintegration time is ~~low~~short. This result is in line with a study by Sri et al. (2018), which found that increasing the amount of MDX ~~would make~~ made the film disintegrate more rapidly ([26]) ~~[21]~~. 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.

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]) ~~[22]~~.

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~~4.00~~% and 10.00~~6.50~~% respectively, with a tensile strength response of 1.50~~81~~ MPa, 104.26~~86.71~~% elongation, and a disintegration time~~period~~ of 82.95~~156~~ seconds. On the foundation

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of the obtained data, it can be stated that sorghum starch modification can increase the use of sorghum's use 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 [aquadest] to a concentration of 24% (w/v), with tThe pH of the solution was adjusted to 6 using HCl (Merck, Germany) and NaOH (Merck, Germany) to pH 6. 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°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 a temperature of 60°C and neutralized using 0.1 M NaOH until the pH reached to pH 6. The solution was then placed into an oven at 50°C in a tin in a thin layer. After drying, the powder was removed, mashed with a blender, and sieved through a 100-mesh sieve.. The MDX-sorghum characterization was then performed [2,5].

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4.2. MDX-Sorghum Characterizsation

4.2.1. Yield value

The resulting MDX-sorghum was weighed entirely, and the yield value was calculated using the following Eequation ([27,28]) [23,24]:

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

4.2.2. Dextrose Equivalent (DE) Value

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In order to calculate the DE value, firstly, the Fehling Factor value was calculated. The DE value started by finding the Fehling factor value by dissolving 2.5 g of glucose was dissolved inwith distilled water and the volume was made upwater up to 1,000 mL with distilled water.; Tthen removing 15 mL of the solution was removed and addeding 5 mL each of Fehling's solutions A and B. The mixture was boiled. and While boiling, it was titrated in a boiling state with glucose solution until it turnedbecame reddish-brown. The amount of titrant required was recorded, and the Fehling fFactor was calculated using the following Eequation ([5,28]): [5,24]:

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

The DE value was then calculated by preparing a 10 g/200 mL solution of MDX-sorghum and inserting 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 athe solution of MDX-sorghum until a reddish brown colour was obtained. The required titrant iswas then recorded, and the DE value iswas calculated using the following Eequation ([5,28]) [5,24]:

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

4.2.3. Solubility

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A total of 0.5 g of the sample was weighted (b) then dissolved in 10 mL of distilled water and before being vortexed for 30 seconds. The solution was then centrifuged for 15 minutes at 3000 rpm. In additionAfter that, 5 mL of the solution supernatant was separated and driedevaporated in an oven at 105-°C until for 5 hours. The product wasis then weighed and the result wasis recorded as weight (a). The solubility (%) of the sample wasis then calculated using the following Eequation ([27,29]) [23,25]:

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

4.2.4. Swelling Power

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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 ~~utilizing~~ Equation ([27]) ~~[23,25]~~:

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

4.2.5. Infra-Red Fourier Transform (FTIR) Analysis

MDX-sorghum was milled~~ground~~ and 2 g of the sample was 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 ~~wave number region~~spectral range of 4,000–400 cm^{-1} ([30,31]).

~~[26,27].~~

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. ODF was produced using the solvent casting method ~~(see Table 6 for composition)~~. First, citric acid (4 g) and sucrose (4 g) were dissolved using distilled water ~~to become~~ (mass A). MDX-sorghum was then added~~dispersed~~ in hot water and was stirred until it dispersed~~expanded, forming~~ (mass B). In hot water, 4 g of Hydroxypropyl Methyl Cellulose (HPMC) (Luxchem, Indonesia) was mixed and dispersed ~~and mixed~~ (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 ~~remaining~~ 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 ~~being~~ heatinged ~~for 24 hours~~ at 50°C for 24 hours. The ~~created~~ obtained film ~~is~~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 ~~percentage~~ 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 ~~is~~was recorded as the disintegration time ([32]) ~~[28]~~.

4.5. Data Analysis

Response data in the form of tensile strength ~~test results~~, elongation, and disintegration times 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]) ~~[17]~~.

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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, ~~percentage~~ elongation, and disintegration time tests were then compared with the predicted RSM data.

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Conflict of interest statement: The authors declare that this article has no actual, potential, or perceived conflict of interest.

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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	72.58%	86.71%

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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

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Table 3. Analysis of ODF Cetirizin HCl Tensile Strength, ~~Percent~~ 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		Liniear	Liniear	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

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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

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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

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Table 6. ODF cetirizine HCl composition based on CCD

Run	Batch	Composition						
		Cetirizine HCl (mg)	MDX-Sorghum* (%)	Glycerol* (%)	Sucrose (%)	Citric Acid (%)	HPMC (%)	Distilled WaterAq ~~uadest~~ ad (mL)
1.	F1	1,500	4.00	6.50	4	4	4	100
2.	F2	1,500	4.00	3.00	4	4	4	100
3.	F3	1,500	4.00	10.00	4	4	4	100
4.	F4	1,500	4.00	6.50	4	4	4	100
5.	F5	1,500	5.41	8.97	4	4	4	100
6.	F6	1,500	4.00	6.50	4	4	4	100
7.	F7	1,500	2.59	8.97	4	4	4	100
8.	F8	1,500	4.00	6.50	4	4	4	100
9.	F9	1,500	6.00	6.50	4	4	4	100
10.	F10	1,500	4.00	6.50	4	4	4	100
11.	F11	1,500	4.00	6.50	4	4	4	100
12.	F12	1,500	2.59	4.03	4	4	4	100
13.	F13	1,500	2.00	6.50	4	4	4	100
14.	F14	1,500	5.41	4.03	4	4	4	100

*CCD-RSM Concentration Design Results

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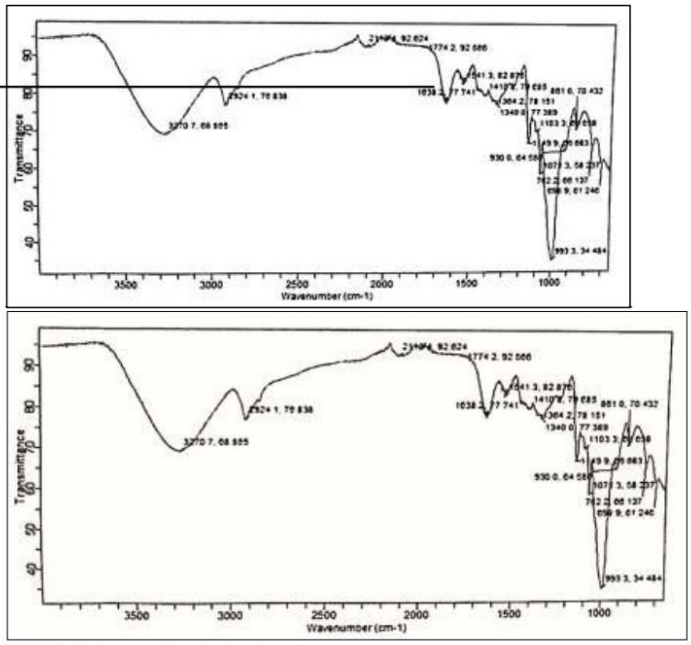

Figure 1. FTIR Spectrum of Sorghum Starch

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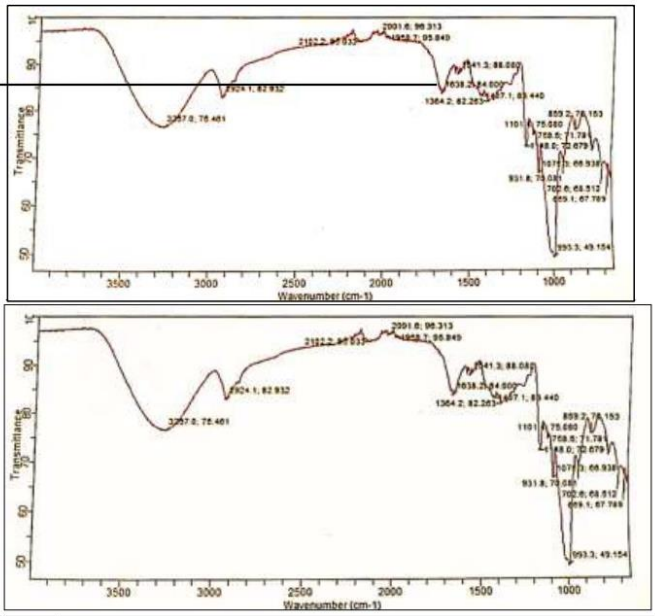

Figure 2. FTIR Spectrum of MDX-Sorghum

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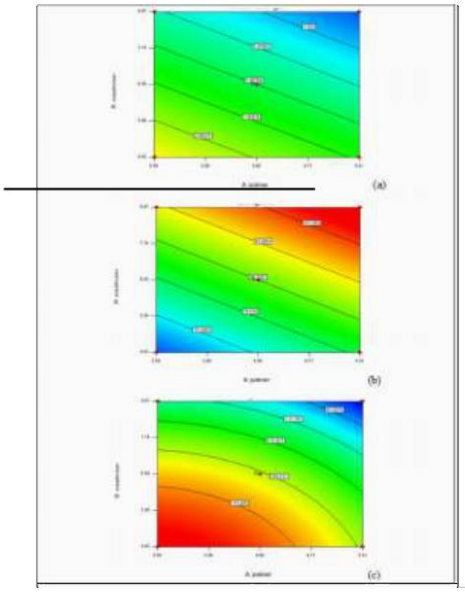

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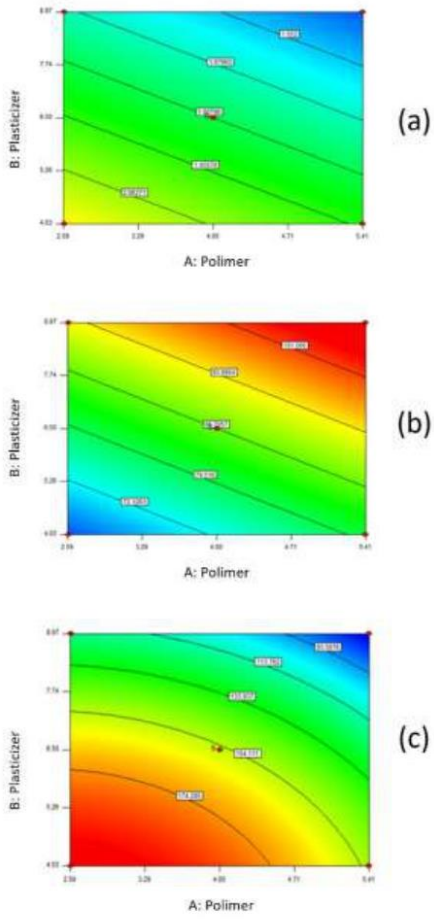

Figure 3. Graph showing the effect of film-forming polymer (MDX-Sorghum) concentration and plasticizer (glycerol) concentration on tensile strength value (a), ~~percentage of~~ elongation (b), and disintegration time (c)

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Paper accepted (28 April 2023)