

DEVELOPMENT OF PRASMAN LEAF SUSPENSION IN COMBINATION WITH PULVIS GUMMI ARABICI AND HYDROXYETHYLCELLULOSE USING SIMPLEX LATTICE DESIGN METHOD

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Abstract

Suspending agents affect the viscosity, storage, and re-dispersal of suspension preparations. This study aims to optimize the combination of suspending agent PGA and hydroxyethylcellulose to obtain the optimum suspension preparation. This suspension formulation uses a computer program design expert version 11 using the Simplex Lattice Design (SLD) method with 2 suspending agents, namely PGA and hydroxyethylcellulose. This SLD method produces 8 formulas. The parameters of these eight formulas were measured including their physical properties, such as organoleptic, pH, viscosity, sedimentation volume, and redispersibility of the preparation. Data were analyzed and produced a graphic equation of each response that gave the optimum suspension formulation. The formula 1 showed optimal parameters, i.e. physical stability, organoleptic stability, the pH of 5, the viscosity value of 59 cP, 0.04 mL sedimentation, and 95% redispersibility value with the concentration of the suspending agent is 6.25% of PGA and 0.775% of hydroxyethylcellulose, and the desirability value of 0.57. The results indicated that the suspension preparation had the characteristics of low viscosity, the particles settle quickly and are easily re-dispersed. Analysis of ANOVA statistical data on viscosity, sedimentation volume, and redispersibility of suspension preparations showed a p-value < 5 or significant meaning that the use of the SLD method affected increasing and decreasing the response value.

Keywords: *Suspending agent, Formulation, Simplex Lattice Design.*

INTRODUCTION

Suspending agent is one of the constituents of suspension preparations that affect the viscosity of the suspension. The suspending agent will slow down the deposition of the active substance particles in the suspension preparation and disperse the insoluble active substance into the carrier liquid (Florensita, 2019). Suspending agents have an important role in maintaining stability during storage, increasing viscosity, and slowing sedimentation (Emilia *et al.*, 2013).

The search for the composition of a dosage formula is the development or formulation of a dosage form. A method, particularly the simplex lattice design (SLD) method, is required to obtain the best formula. The simplex lattice design approach is computer software that searches for dosage formulations by altering the preparation's

composition in order to acquire the optimal formula composition and the highest dose desirability value (Bahri, 2016).

Researchers were drawn to the simplex lattice design method to explore the formulation of suspension preparations, particularly the suspension of Prasman leaf extract (*Eupatorium triplinerve* Vahl.) with a suspension agent combination of PGA and hydroxyethylcellulose. The goal of this research was to compare the suspending agents PGA and Hydroxy Ethyl Celulosa in the suspension preparation of Prasman leaf extract so that the most stable preparation could be obtained.

RESEARCH METHODOLOGY

Equipment

Program design expert version 11, digital scale (Ohaus), digital viscometer (NDJ-8s),

Table 1. Limitations of the use of PGA and Hydroxyethylcellulose used as a suspending agent.

Suspending Agent	Concentration	
	Lower limit (%)	Upper limit (%)
PGA	5	10
HEC	0,1	1

Table 2. The proportion of PGA and Hydroxyethylcellulose in the formula from Design-Expert version 11

Suspending agent	F1	F2	F3	F4	F5	F6	F7	F8
PGA	1	0.25	0.5	1	0	0.5	0	0.75
HEC	0	0.75	0.5	0	1	0.5	1	0.25

mortars, stampers, 60 mL bottles, and glassware.

Materials.

Prasman leaf extract, PGA (pulvis gummi arabicum), hydroxyethylcellulose, peppermint oil, benzoic acid, sorbitol 70%, ethanol 96%, distilled water.

Preparation of leaf extract of Prasman

Prasman leaf (*Eupatorium triplinerve* Vahl.) by weighing 500 grams of coarse powder, put in a macerator container, and macerated with 2.5 L of 96% ethanol in a ratio of 1:5 for 5 days in a tightly closed glass container and protected from direct sunlight, stirred every day for 1 hour. After 5 days the liquid extract filtrate was filtered to get the filtrate (filtrate 1) and residue. The residue was then re-macerated with 1 L 96% ethanol for 3 days and stirred every day for 1 hour, then after 3 days the maceration extract filtrate was filtered and obtained filtrate 2. Filtrate 1 and filtrate 2 were combined, and the filtrate was evaporated using a rotary evaporator at a temperature of 60°C to obtain a thick extract. Then the extract was dried in an oven at 60 °C to obtain a dry extract. The dry extract was weighed and stored in a tightly closed container.

Optimization of the suspending agent

Suspending agent optimized with Design-Expert software version 11.1.2.0 with the Simplex Lattice Design method. The initial formula for suspension preparations was determined with PGA in a concentration

range of 5-10% and hydroxyethyl cellulose in a concentration range of 0.1-1%. The data was then loaded into the Design-Expert software version 11.1.2.0 using the Simplex Lattice Design method to generate 8 formulas, which were then tested for viscosity, sedimentation volume, and redispersibility. Considering the lower and higher limits, the concentration ratio of PGA and Hydroxyethyl cellulose was calculated. The combination suspending agent PGA has a concentration of 5-10% and hydroxyethyl cellulose has a concentration of 0.1-1 percent (Table 1) (Rowe, 2009).

The ratio of PGA and hydroxyethyl cellulose in the formula was also established using Design-Expert software version 11 and the simplex lattice design approach, yielding 8 formulae with PGA and Hydroxyethylcellulose concentrations as shown in Table 2.

The complete composition of suspending agents from formula 1 to formula 8 can be seen in Table 3. The complete formula design of the 8 Prasman leaf extract suspension formulations studied and the function of each component can be listed in Table 4.

All ingredients were weighed, and PGA was dissolved in a mortar with water, 7 times the weight of PGA. The hydroxyethyl cellulose was sprinkled into hot water as much as 20 times the weight of the hydroxyethyl cellulose and allowed to swell in another mortar. Then propylene glycol was added into the PGA and hydroxyethyl

Table 3. Composition of suspending agents

Suspending agent	Composition of suspending agent (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
PGA	1	6,25	7,5	10	5	7,5	5	8,75
HEC	0,1	0,775	0,55	0,1	1	0,55	1	0,325

Table 4. Formulation design

Ingredients	Formulation design (%)								Function
	F1	F2	F3	F4	F5	F6	F7	F8	
PGA	10	6.25	7.5	10	5	7.5	5	8.75	Suspending agent
HEC	0.1	0.775	0.55	0.1	1	0.55	1	0.325	Suspending agent
Propyleneglycol	25	25	25	25	25	25	25	25	Wetting agent
Peppermint oil	4 gtt	4 gtt	4 gtt	4 gtt	4 gtt	4 gtt	4 gtt	4 gtt	Button
Sorbitol	20	20	20	20	20	20	20	20	Sweetener
Benzoic acid	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	Preservative
Phosphate buffer pH 6	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	Buffer
Distilled water	100	100	100	100	100	100	100	100	Carrier fluid

cellulose solution, stirring until homogeneous. Then, sorbitol and benzoic acid were added, stirred until homogeneous, added with phosphate buffer pH 6 and peppermint oil flavoring, stirred until homogeneous, and added with distilled water to 100 mL (Suryani *et al.*, 2019).

Evaluation of Prasman leaf extract suspension preparations

Viscosity test

The viscosity of the suspension preparation was measured using a digital viscometer (NDJ-8s) by immersing the viscometer spindle in 100 mL of the preparation at the appropriate speed. The results of the viscosity of the preparation were seen on the scale on the tool after stability was achieved. To determine the stability of the preparation, the viscosity test was carried out once every 7 days for 30 days. The standard for the good suspension viscosity is 37-396 mPas (Konijn *et al.*, 2014).

Sedimentation volume of Prasman leaf extract suspension.

The suspension of the ethanolic extract of Prasman leaves was put in a 10 ml measuring cup for 4 weeks without treatment, recorded

the initial volume (Vo), and the sedimentation volume was evaluated every 7 days without stirring until the sedimentation height was constant (Emilia *et al.*, 2013). Sedimentation volume (F) is one of the sedimentation parameters of a suspension. The sedimentation volume was calculated using equation 1 (Nyandoro *et al.*, 2019).

$$F = \frac{Vu}{Vo} \dots\dots (1)$$

F: Volume of sedimentation (mL)

Vu: Final volume of sedimentation (mL)

Vo: Initial volume of preparation (mL)

Redispersibility test of Prasman leaf extract suspension.

The redispersibility test was carried out manually by rotating the suspension from the sedimentation volume test at 180°C and inverted to its original position, with a value of 100% if the suspension was completely dispersed. If each suspension reversal has not been completely dispersed, then there is a reduction of 5% from the total suspension preparation (Suena, 2020; Kadiri and Okafor, 2010)

Data analysis

Data analysis was carried out on the parameters of the leaf extract suspension preparation, i.e. viscosity, sedimentation volume, and redispersibility. Data analysis used software design expert version 11.1.2.0 to get the optimum formula. ANOVA test was carried out on the values of viscosity, sedimentation volume, and redispersibility. with a significant assessment if the p-value <0.05 with a 95% of confidence level.

RESULTS AND DISCUSSION

Suspension is a liquid solution that contains tiny medication particles that are insoluble in water (Anggreini, 2013). The suspending agent PGA was combined with hydroxyethyl cellulose to create a suspension of Prasman leaf extract. The reason for using PGA is that it is easily soluble in water, produces a thick and translucent solution, does not change the chemical structure, and is natural (Anjani *et al.*, 2011), whereas hydroxyethyl cellulose is non-toxic, can be mixed with a variety of materials, and has good stability and viscosity (Anjani *et al.*, 2011; Rowe, 2009).

It is critical to test the viscosity of the preparation. The viscosity of a suspension explains its flow and the physical factors that must be monitored, as the viscosity of a suspension can affect redispersibility, dose, and pouring ease. High viscosity is not expected because it will be difficult to pour and re-disperse the suspension (Artania *et al.*, 2020). According to the test results, three formulas, namely formulas I, IV, and VIII, do not meet the requirements because their viscosity is less than 37cP, refer to the SNI viscosity criterion is between 37-396 cP (Konijn *et al.*, 2014).

The flow type of Prasman leaf extract suspension was pseudoplastic flow, in which the shearing rate and shearing stress were not linearly related and viscosity changes. Asymmetrical particles with various contact points generate a three-dimensional network throughout the preparation in liquids with a pseudoplastic flow type. As a result, this

structure gives a gel-like preparation a rigid shape, whereas when the sample is poured or pressed out of the container or a force is applied, flow begins because the rigid three-dimensional structure begins to break or the point of contact is disrupted, causing the particles to line up. The consistency of pseudoplastic flow qualities in the container is rather high, although it may be poured and dispersed readily (Melian, 2018).

The viscosity parameter has a significance value of 0.0001 or p0.05 in the ANOVA statistical analysis, indicating that an increase or reduction in the concentration of PGA and hydroxyethylcellulose had a significant effect on the viscosity value. The obtained R2 value is 0.9817. The R2 value is around 1, indicating that the response data is approaching the model. The results show that the variation of the suspending agent component and the response have a substantial relationship. The viscosity of the suspension affected the PGA and hydroxyethylcellulose components. The component equation is changed below, and the response displayed in equation 2 is changed.

$$Y = 28.09(A) + 65.65 (B) + 3.45 (AB) \dots \dots (2)$$

Y = Sedimentation volume

A = Level of PGA

B = Level of HEC

Component A (PGA), component B (Hydroxyethylcellulose), and a mixture of components A and B have positive coefficient values. This means that the regression equation depicts the predicted effect; if the component is raised, the responsibility will grow as well. The size of the number denotes the magnitude of the component's effect on the answer (Yu *et al.*, 2016). The graph obtained takes the following shape (Figure 1):

The association between variable A (PGA) and component B (hydroxyethyl cellulose) was shown in Figure 1. Variable A has a coefficient of +28.09, while variable B has a coefficient of +65.65, indicating that using hydroxyethyl cellulose as a single suspending agent has a major influence on raising viscosity, and the higher the

concentration of hydroxyethyl cellulose, the higher the viscosity.

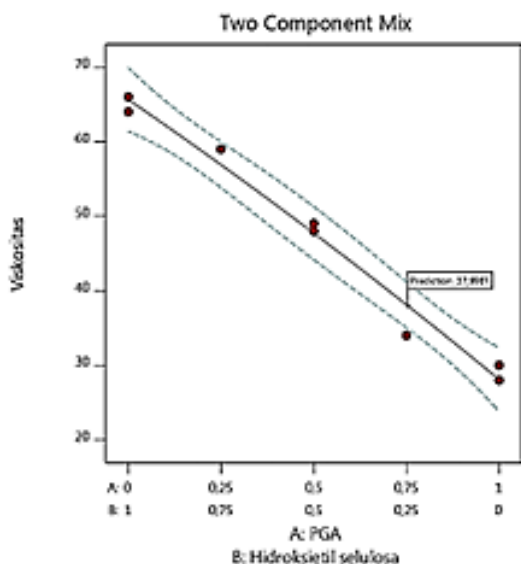


Figure 1. Graph of the relationship between variables and viscosity

The height of sediment generated from preparations that had previously been disseminated and allowed to stand for 30 days was determined by observing the volume of sedimentation (Wahyuni *et al.*, 2020). After 30 days of storage, the sedimentation volume of Prasman leaf extract suspension ranged from 0.06 to 0.1 mL, with 8 formulae having sedimentation volumes that met the requirements.

The sedimentation volume response showed a significance value of 0.0017 or $p < 0.05$ after the ANOVA analysis, indicating that an increase or reduction in PGA and hydroxyethylcellulose concentrations had a significant effect on the sedimentation volume value. The obtained R^2 value is 0.9227. The closeness of the R^2 value to 1 implies that the response data is approaching the model. The results show that the various components (PGA and hydroxyethylcellulose) have a strong association with the sedimentation volume response. Equation 3 shows the equation for the relationship between the various components and the response.

$$Y = 0.0535 (A) + 0.1002 (B) + 0.0173 (AB) \dots (3)$$

Y= sedimentation volume
 A= Proportion of PGA
 B= Proportion of HEC

The coefficient values of variable A (PGA), variable B (Hydroxyethylcellulose), and the proportion of the mixture of the two (AB) are all positive, indicating that the regression equation above indicates the expected effect, i.e., increasing the variable will increase the responsibility. The graphic form achieved is as follows (Figure 2).

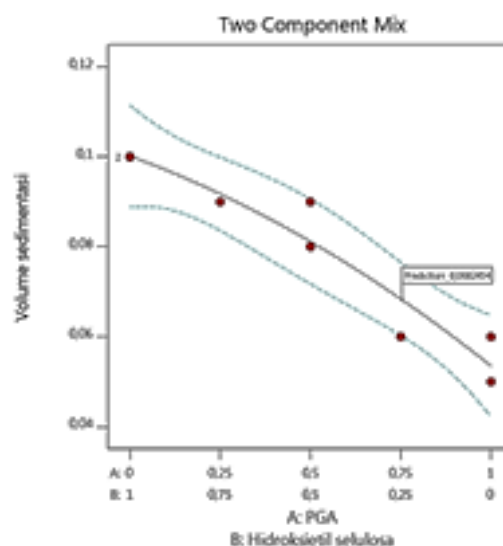


Figure 2. Graph of the relationship between variables and sedimentation volume

The link between variable A (PGA) and variable B (HEC) is depicted in Figure 2. Variable A has a coefficient of +0.0535, while variable B has a coefficient of +0.1002. Because hydroxyethyl cellulose has a higher viscosity, Variable B has a stronger influence on raising sedimentation volume. The sedimentation volume is affected by the viscosity level, with the greater the viscosity value, the larger the sedimentation volume created. Meanwhile, due to its low viscosity, PGA has little effect on the preparation's sedimentation volume.

The interaction between variables A and B is positive (+0.0173), indicating that viscosity impacts sedimentation volume, with a higher

viscosity value resulting in a larger sedimentation volume. Meanwhile, due of its low viscosity, PGA has little effect on the sedimentation volume of the preparation. The interaction between variables A and B is positive (+0.0173), indicating that increasing it will raise the response value, resulting in a higher sedimentation volume.

The purpose of the redispersibility test is to see if the suspension can be entirely re-dispersed with minimal shaking after being stored. One of the characteristics that must be carried out in research to assure consistency of a preparation is the redispersibility test. The viscosity value influences redispersibility; if the preparation has a high viscosity, the redispersibility ability is low, causing caking and a non-homogeneous dosage (Anggraeni, 2013). The findings of the redispersibility test revealed that the eight suspension formulae can be easily re-dispersed. 1x revolution (180°) is the number of revolutions required to re-disperse the suspension preparation. The redispersion value decreases by 5% with each test repeat, but all formulas have a respectable redispersion value.

The significance value of 0.0102 or p0.05 was obtained from the ANOVA statistical analysis of the redispersibility response, indicating that an increase or reduction in the concentration of PGA and hydroxyethylcellulose had a significant effect on redispersibility. The obtained R2 value is 0.8402. When the R2 number is close to 1, it means that the response data is approaching the model. The results show that the various variables (PGA and hydroxyethylcellulose) have a strong association with the redispersibility response. Equation 4 shows the equation for the relationship between the variable that is varied and the response.

$$Y = 95.74(A) + 82.40(B) - 8.63(AB) \dots (4)$$

Y= Redispersibility
 A= Proportion of PGA
 B= Proportion of Hydroxyethylcellulose

The coefficient values of variables A (PGA) and B (hydroxyethylcellulose) are positive, but the proportion of the mixture of the two variables (AB) is negative, indicating that the regression equation above depicts the expected effect, i.e., lowering the component will result in a lower response. The magnitude of the number produced reflects the amount of the variable's effect on the response, and the negative value indicates the antagonistic effect between the components and the response. The link between variable A (PGA) and variable B (hydroxyethylcellulose) is depicted in Figure 3.

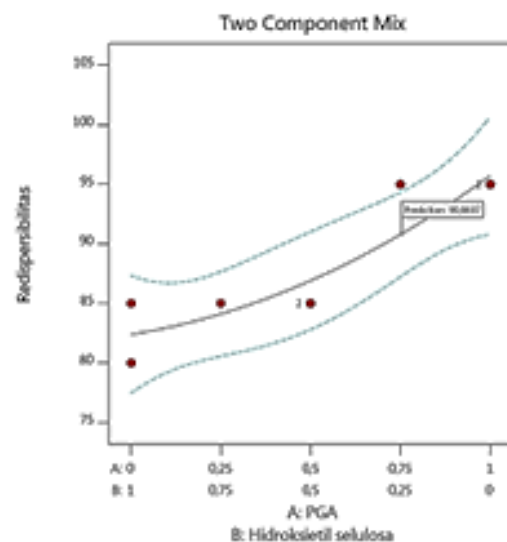


Figure 3. Graph of the relationship between variables with redispersibility

Variable A has a coefficient of (+95.74) and variable B has a coefficient of (+82.40). Because PGA has a lower viscosity value than hydroxyethyl cellulose, the preparation can be easily re-dispersed, whereas hydroxyethylcellulose has a lower coefficient value than PGA. The higher the hydroxyethyl cellulose concentration, the lower the redispersibility; high viscosity is difficult to redisperse; and the interaction of variables A and B has a coefficient value of -8.63, indicating that the interaction of variables A and B can reduce the redispersibility of suspension preparations.

Determination of optimum formula of suspension of buffet leaf extract.

The optimum formula is developed by assessing the results of testing the physical properties of the preparation using the program Design-Expert version 11 to generate a graph of each reaction and obtain the optimum formula.

The suspension preparations' viscosity was decreased to a minimum so that they could be easily re-dispersed. The goal of maximum redispersibility is achieved by a suspension with excellent dispersion ability and little shaking. The goal of maximizing sediment volume is to achieve the highest possible sedimentation volume in the suspension. The recommendations produced from the investigation have a level of desirability, as shown in Figure 4.

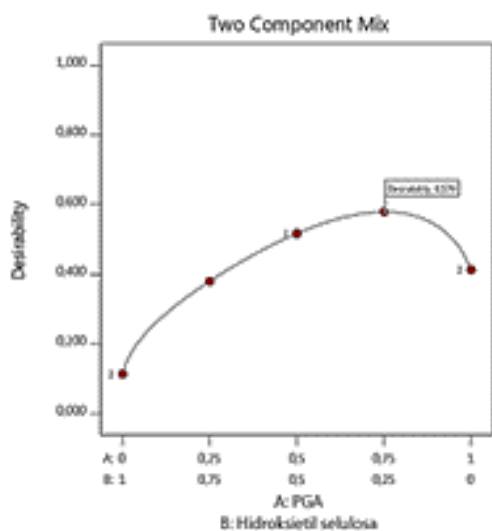


Figure 4 Desirability curve

The desirability value is a numerical representation of the desired model. A rating

close to 1 indicates high desirability (Damayanti *et al.*, 2018).

The best formula with 6.25 percent PGA composition: hydroxyethyl cellulose 0.775 percent with the maximum attractiveness value of 0.579 is shown in Figure 4. The physical attributes of the optimum formula are predicted to be around 58 percent based on this attractiveness value. The software design expert not only predicts the ideal formula, but also the expected response value from the optimum formula.

The best formula was confirmed by using the Simplex Lattice Design approach to formulate the formula proposed by the Design-Expert software. Physical qualities of the preparations are examined to prove and validate the data anticipated by the software and to determine whether the results produced are correct. The viscosity is anticipated to be 38.002 cP, the sedimentation volume to be 0.068 mL, and the redispersibility to be 90.842 percent.

CONCLUSION

In conclusion, the optimum formula of Prasman leaf extract was obtained with a ratio of PGA and hydroxyethylcellulose was 6.25%:0.775%, with a desirability value of 0.579. The addition of suspending agent PGA and hydroxyethylcellulose, as well as their interaction, gave a positive effect by increasing the physical properties of the suspension of Prasman leaf extract on viscosity, sedimentation volume, and redispersibility.

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