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Orally Disintegrating Film formulation of standardized extract of red ginger (*Zingiber officinale* var. Rubrum)

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ABSTRACT

Red ginger (*Zingiber officinale* var. Rubrum) is a biopharmaceutical plant that contains 6-gingerol, 6-shogaol, and galanolactone. The preparation of red ginger in traditionally allowed its development. One of them is making it into Oral Disintegrating Films (ODFs). ODFs is a very thin film that will immediately disintegrate if placed on the tongue so it can provide a faster effect. This research aims to formulate red ginger extract as an ODF. Red ginger extract is used as an active ingredient. The polymers to be chosen are HPMC (Hydroxypropyl methylcellulose) K4M and HPMC E3. The plasticizers to be chosen are glycerin, polyethylene glycol (PEG 400), and Propylene glycol (PG). Sucrose is used as a sweetener agent and sodium benzoate as a preservative. The method we used for making ODFs is solvent casting. The evaluations of ODFs are organoleptic, weight measurement, film thickness, disintegration time, and swelling power. The results showed that the ODFs preparation of red ginger extract with 2% HPMC K4M and 30% PEG 400 from polymer formed a film that met the requirements. The weight of the film is 0.027 ± 0.003 g, the thickness of the film is 0.063 ± 0.008 mm, the disintegration time of the film using the petri dish method is 25.03 ± 2.41 seconds, with the frame method is 5.45 ± 0.39 seconds, and the swelling index in 10 seconds is $146.1 \pm 4.7\%$.

Keywords: ODF, red ginger extract, HPMC K4M, PEG 400.

1. INTRODUCTION

Red ginger (*Zingiber officinale* var. Rubrum) is a biopharmaceutical plant that is widely cultivated in Indonesia. The main compounds contained in red ginger are gingerol and shogaol. This compound has biological activity as an anti-inflammatory, antiemetic, antioxidant, and immunomodulator (Simarmata, 2022). People generally use red ginger as a kitchen spice. Moreover, people also consume red ginger as a

medicine by boiling the rhizomes. One of the efforts to develop traditional medicine is to make red ginger into a pharmaceutical dosage form as an Oral Disintegrating Film (ODF). ODF is a skinny film that will immediately disintegrate and release active substances that will be absorbed by the oral mucosa if placed on the tongue.

Some will be swallowed together with saliva, absorbed in the digestive tract (Liew et al., 2014). Using ODF does not require water, making it easier for patients with difficulty swallowing medication and traveling to consume it. ODF preparations are composed of active substances, polymers, and plasticizers (Pacheco et al., 2021). The polymers commonly used are hydrophilic polymers, such as HPMC (Liew et al., 2014). HPMC is a powder, creamy or white in color, odorless, and tasteless. HPMC is non-toxic, water-soluble, and forms a good film layer. HPMC has various viscosities (HPMC K4M - 4000 cPs, HPMC E3 - 3 cPs) (Guarve and Kriplani, 2021). According to a previous study by HPMC forms a smooth film surface, free of air bubbles, and is easy to release from molds (Febriyenti et al., 2010).

The prerequisites for selecting a suitable polymer for ODF preparations are compatibility with the active ingredient, film-forming ability, quick disintegration, water solubility, non-toxicity, and non-irritation (Carvalho et al., 2023). The main component of ODF is the plasticizer. The function of a plasticizer in ODF formulas aims to modify the physicochemical properties of the polymer, resulting in a good film that is easy to remove from the molds (Vuddanda et al., 2017). Moreover, the type and concentration of plasticizer can also affect the characteristics of the film. Some materials that can act as plasticizers include glycerin, PEG (Polyethylene Glycol) 400, and PG (Propylene Glycol) (Kaur and Garg, 2018; Sun et al., 2018).

2. MATERIALS AND METHODS

Ingredients

The ingredients used in this research were red ginger (*Zingiber officinale* Var. Rubrum) obtained from the Bari Village, Padang Pariaman. HPMC was bought from Lawsim Zecha. Glycerin was obtained from PT. Palapa Muda Perkasa, West Java. PG (Propylene Glycol) was obtained from Baratachem, Indonesia. PEG (Polyethylene Glycol) 400 was obtained from Alpha Chem, Tangerang. Stevia was bought from PT. Tatarasa Primatama, Tangerang. Sucrose was obtained from JT Baker, USA. Sodium benzoate was obtained from Gloria Interchem, India. Ethanol and distilled water were obtained from Andeska, Padang.

Preparation and Standardization of Red Ginger Extract

Red ginger extract was prepared and standardized according to the methods in FHI, (2017) & Suharti et al., (2017).

Selection of Polymer

A pre-gel was prepared using HPMC E3 and HPMC K4M polymers (Table 1). Each polymer was prepared at concentrations of 2%, 3%, and 6%.

Table 1 The composition of the red ginger extract pre-gel for polymer selection

Ingredient	FA1	FA2	FA3	FB1	FB2	FB3
Red ginger extract (mg)	163	163	163	163	163	163
HPMC K4M (mg)	200	300	600	-	-	-
HPMC E3 (mg)	-	-	-	200	300	600
Glycerin (mg)	60	90	180	60	90	180
Sucrose (mg)	200	200	200	200	200	200
Sodium benzoate (mg)	10	10	10	10	10	10
Distilled water up to (g)	10	10	10	10	10	10

*Compositions in the table are for 1 mold (a petri dish with a diameter of 9.1 cm).

Red ginger extract ODF is prepared using the solvent casting method. HPMC is homogenized with glycerin and red ginger extract and then the sweeteners and preservatives are dissolved in deionized water were added. The mixture is homogenized using an ultraturrax at 6000 rpm for 5 minutes. It is then allowed to sit at room temperature until no air bubbles are present. Afterward, it is

poured into molds. The pre-gel is then dried at room temperature for 24 hours. Once dry, the red ginger extract ODF is carefully removed from the molds. The red ginger extract ODF is cut into 2x2 cm² pieces, containing 10 mg of red ginger extract.

Selection of Plasticizer

After obtaining the polymer selection results, the chosen polymer (HPMC K4M) is used in the plasticizer selection phase. The plasticizers used in this research are glycerin, PEG 400, and PG. The concentration of each plasticizer in the formula is 10% and 30% of the amount of polymer used. The procedures for preparing the pre-gel and red ginger extract ODF are the same as in the polymer selection phase (Table 2).

Table 2 The composition of the red ginger extract pre-gel for plasticizer selection

Ingredient	FC1	FC2	FD1	FD2	FE1	FE2
Red ginger extract (mg)	163	163	163	163	163	163
HPMC K4M (mg)	200	200	200	200	200	200
Glycerin (mg)	20	60	-	-	-	-
PEG 400 (mg)	-	-	20	60	-	-
PG (mg)	-	-	-	-	20	60
Sucrose (mg)	200	200	200	200	200	200
Sodium benzoate (mg)	10	10	10	10	10	10
Distilled water up to (g)	10	10	10	10	10	10

* Compositions in the table are for 1 mold (a petri dish with a diameter of 9.1 cm).

Evaluation of Red Ginger Extract ODF

Organoleptic

Evaluation organoleptic testing involves observing the homogeneity, color, odor, texture, and taste of the ODF preparation (Irfan et al., 2016).

Measurement of Weight and Thickness of ODF

Weight evaluation of ODF is performed by individually weighing six randomly selected red ginger extract ODF. The thickness of ODF is measured using a digital micrometre (Krisbow®) on six red ginger extract ODF from each formula.

Measurement of pH of ODF Preparation

The pH measured is that of the pre-gel that has been prepared. The instrument used for pH measurement is a pH meter (Mettler Toledo®). The electrode is immersed in the pre-gel until it shows a constant pH reading. This is done with 6 repetitions (Kalyan and Bansal, 2012).

Moisture Content of ODF

The moisture content of ODF is measured using a moisture balance instrument at a temperature of 105°C. The acceptable criterion is <10% (Han et al., 2019).

Swelling Index

The initial weight of an ODF is denoted as W₀. The ODF is allowed to swell in 15 ml of phosphate buffer at pH 6.8 in a petri dish for 15 seconds. Repeat the immersion until a constant weight (W_t) is achieved. Calculate the swelling index using the following equation:

$$\text{Swelling Index (\%)} = (W_t - W_0) / W_0 \times 100\%$$

Where: W_t = Weight of the film at time t; W₀ = Weight of the film at time 0 (Arya et al., 2010).

Disintegration Time

The requirement for ODF disintegration time is less than 60 seconds. There are two methods to determine this parameter:

Slide frame method: A 2x2 cm red ginger extract ODF is held with tweezers. Then, one drop of deionized water is placed on the red ginger extract ODF, and the time it takes for a hole to form in the red ginger extract ODF is recorded (Li and Castillo, 2020).

Petri dish method: A 2x2 cm red ginger extract ODF is placed in a petri dish containing 6 mL of deionized water. Record the time it takes for the ODF to completely dissolve (Simarmata, 2022).

3. RESULTS & DISCUSSION

Red ginger extract was prepared and standardized based on (FHI, 2017; Suharti et al., 2017). The results of standardization of red ginger extract obtained were thick extracts, yellow-brown in color, distinctive odor, and spicy taste. The yield obtained was 18.21%. The water content obtained was $9.50\% \pm 0.71$. The total ash content obtained was $1.04\% \pm 0.36$. The retention factor (Rf) value obtained was 0.46, while the Rf for the 6-gingerol comparison was 0.46. The standardized extract is then formulated into ODF preparation. The procedure begins with the polymer selection stage. Polymer selection stage aims to select a polymer that could mix with red ginger extract and could produce ODF that meets the requirements. The polymers used in this study were HPMC K4M and HPMC E3.

Table 3 Result of the Polymer Selection Stage

Formula	Pre-Gel	ODF	Mean $\pm$ SD (mm)
FA1	The mixture is dark yellow, slightly viscous, and can be spread evenly in a petri dish	A film is formed, homogeneous, the film texture is smooth, and opaque	0.062 ± 0.011
FA2	The mixture is dark yellow, slightly viscous, and can be spread evenly in a petri dish	A film is formed, homogeneous, the film texture is smooth, and opaque	0.070 ± 0.011
FA3	Thick dispersion that cannot be poured evenly into the mold	No film formed	No film formed
FB1	The mixture is very liquid so it is difficult to dry	No film formed	No film formed
FB2	The mixture is very liquid so it is difficult to dry	No film formed	No film formed
FB3	The mixture is light yellow that easily to be poured and spread evenly in petri dish	A film is formed, not homogeneous, transparent, and has a smooth film texture	0.072 ± 0.003
Comparison	-	A film is formed, homogeneous, and the film texture is smooth,	0.042 ± 0.003

Note: Repetition (n) = 6

Comparison = "G" films candy

FA1 = HPMC K4M 2%

FA2 = HPMC K4M 3%

FA3 = HPMC K4M 6%

FB1 = HPMC E3 2%

FB2 = HPMC E3 3%

FB3 = HPMC E3 6%

From the results in Table 3, it can be concluded that HPMC K4M 2% is the selected polymer. This occurs due to differences in the viscosity of each type of polymer. The viscosity of HPMC K4M is 4000 cps. Meanwhile, HPMC E3 has a viscosity of 3 cps. The higher viscosity of HPMC K4M also functions as a dispersant so that it can be relatively homogeneous with the active substance. HPMC K4M has a greater molecular weight than HPMC E3 specifically 4,000,000. HPMC K4M 2% produced film with a thickness close to the thickness of the comparison film (Figure 1).

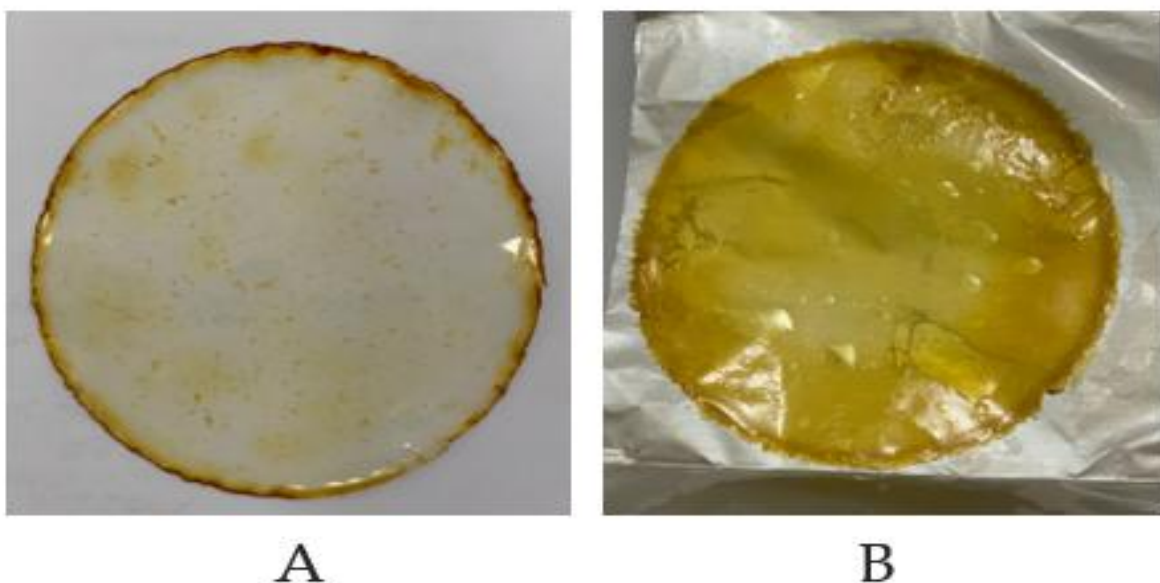


Figure 1 Results of polymer selection, A. HPMC E3, B. HPMC K4M

The next stage is the selection of a plasticizer. The plasticizers used were glycerin, PEG 400, and PG with two variations in concentration (10% and 30% of the total polymer). All formulas produce a film that is easily removed from the mold. The following are the results of the plasticizer selection stages (Figure 2).

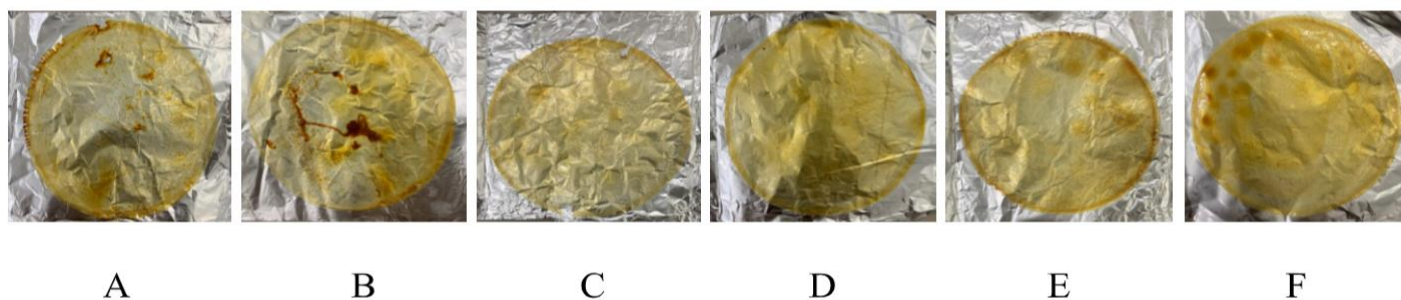


Figure 2 Photographs of red ginger extract ODF using some plasticizers, A. Glycerin 10%, B. Glycerin 30%, C. PEG 400 10%, D. PEG 400 30%, E. PG 10%, F. PG 30%

The selected plasticizer can be homogeneous with the active ingredient and the polymer. Based on the evaluation results of the plasticizer selection stage in Table 4, it is shown that PEG 400 at 30% concentration is the selected plasticizer. The results of the uniformity of weights for each ODF must not deviate from the average ODF weight. The ODF thickness evaluation results for each formula meet the requirements in the range of 0.005-0.200 mm (Kaur and Garg, 2018). Differences in plasticizer and concentration affect film thickness. The higher the plasticizer concentration, the thicker the film produced (Lee et al., 2017).

pH measurement is described as the process of the ODF surface when it comes into direct contact with saliva which has a pH of 6.8 - 7.2. The pre-gel mass that forms ODF has a pH below the pH of saliva, and irritation of the mucosa will occur. The pH evaluation

results for all formulas in Table 5 ranged from 5.973 – 7.197. With this pH range, there is little chance of irritation of the oral mucosa. The measurement of moisture content is aimed at determining the moisture content in ODF. A low moisture content makes the film brittle, whereas a high moisture content supports microbial growth (Vuddanda et al., 2017). Based on the moisture content evaluation results in Table 5, the moisture content increases with a higher concentration of plasticizer.

Table 4 Evaluation Result of the Selection Plasticizer Stage

Category	FC1	FC2	FD1	FD2	FE1	FE2
Homogeneity	Inhomogeneous	Inhomogeneous	Relatively homogeneous	Homogeneous	Relatively homogeneous	Inhomogeneous
Scent	Specific	Specific	Specific	Specific	Specific	Specific
Color	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Flavor	Slightly spicy	Slightly spicy	Slightly spicy	Slightly spicy	Slightly spicy	Slightly spicy
Texture	Smooth, oily, not transparent, easy to remove from mold.	Smooth, oily, not transparent, easy to remove from mold.	Smooth, slightly oily, not transparent, easy to remove from mold	Smooth, slightly oily, not transparent, easy to remove from mold	Smooth, slightly oily, not transparent, easy to remove from mold	Smooth, oily, non-transparent, non-elastic, flexible

Note: Comparison = "G" films candy

FC1 = HPMC K4M 2% + glycerin 10% of the polymer

FC2 = HPMC K4M 2% + glycerin 30% of the polymer

FD1 = HPMC K4M 2% + PEG 400 10% of the polymer

FD2 = HPMC K4M 2% + PEG 400 30% of the polymer

FE1 = HPMC K4M 2% + PG 10% of the polymer

FE2 = HPMC K4M 2% + PG 30% of the polymer

Table 5 Evaluation Results of ODF Weight, ODF Thickness Uniformity, ODF Pre Gel pH, ODF Moisture Content

Formula	Weight mean $\pm$ SD (g)	Thickness mean $\pm$ SD (mm)	Film pH mean $\pm$ SD	Film moisture mean $\pm$ SD
FC1	0.020 $\pm$ 0.011	0.061 $\pm$ 0.008	7.197 $\pm$ 0.010	7.655 $\pm$ 0.369
FC2	0.033 $\pm$ 0.003	0.064 $\pm$ 0.007	7.132 $\pm$ 0.007	8.421 $\pm$ 0.214
FD1	0.023 $\pm$ 0.003	0.051 $\pm$ 0.003	7.047 $\pm$ 0.005	7.335 $\pm$ 0.255
FD2	0.027 $\pm$ 0.003	0.063 $\pm$ 0.008	6.903 $\pm$ 0.008	6.787 $\pm$ 0.225
FE1	0.023 $\pm$ 0.002	0.051 $\pm$ 0.008	6.033 $\pm$ 0.008	7.041 $\pm$ 0.185
FE2	0.026 $\pm$ 0.004	0.057 $\pm$ 0.015	5.973 $\pm$ 0.010	7.605 $\pm$ 0.286
Comparison	0.048 $\pm$ 0.019	0.042 $\pm$ 0.003		

Note: Comparison = "G" films candy

FC1 = HPMC K4M 2% + glycerin 10% of the polymer

FC2 = HPMC K4M 2% + glycerin 30% of the polymer

FD1 = HPMC K4M 2% + PEG 400 10% of the polymer

FD2 = HPMC K4M 2% + PEG 400 30% of the polymer

FE1 = HPMC K4M 2% + PG 10% of the polymer

FE2 = HPMC K4M 2% + PG 30% of the polymer

Based on Table 6, the ODF of each formula produces the largest swelling index in sequence, namely FE1, FE2, FC1, FC2, FD1, and FD2. The different plasticizers for each formula influence the results of the swelling index. The swelling index describes the ability of a polymer to undergo hydration (Barot et al., 2021). Red ginger extract ODF disintegrates quickly in less than 60 seconds when placed in the mouth (Pacheco et al., 2021). This evaluation was carried out to provide an overview of when the ODF experienced disintegration

Table 6 Evaluation Results of the Swelling Index

Time Second	Average film swelling index $\pm$ SD (%)					
	FC1	FC2	FD1	FD2	FE1	FE2
5	170.7 $\pm$ 8.9	134.0 $\pm$ 3.8	129.7 $\pm$ 7.3	117.8 $\pm$ 4.2	200.0 $\pm$ 4.0	190.1 $\pm$ 5.6
10	191.5 $\pm$ 2.6	162.5 $\pm$ 7.0	155.0 $\pm$ 6.1	146.1 $\pm$ 4.7	233.3 $\pm$ 6.1	205.9 $\pm$ 4.1
15	205.9 $\pm$ 7.4	185.9 $\pm$ 3.4	181.9 $\pm$ 5.6	178.5 $\pm$ 4.7	265.4 $\pm$ 5.6	208.6 $\pm$ 13.0
20	221.4 $\pm$ 10.3	Solved	220.3 $\pm$ 15.8	208.8 $\pm$ 16.0	298.7 $\pm$ 2.2	211.1 $\pm$ 3.7

Note: Repetition (n) = 3

FC1 = HPMC K4M 2% + glycerin 10% of the polymer

FC2 = HPMC K4M 2% + glycerin 30% of the polymer

FD1 = HPMC K4M 2% + PEG 400 10% of the polymer

FD2 = HPMC K4M 2% + PEG 400 30% of the polymer

FE1 = HPMC K4M 2% + PG 10% of the polymer

FE2 = HPMC K4M 2% + PG 30% of the polymer

Petri dish method evaluation with the fastest disintegration speed in Table 7 is FD1, FD2, FE2, FE1, FC1, and FC2. Meanwhile, the slide frame method with the fastest destruction time is FD1, FD2, FE2, FE1, FC1, and FC2. Red ginger extract ODF with PEG 400 plasticizer has a short disintegration time. FD1, FD2, FE1, and FE2 met the requirement of the disintegration time.

Table 7 Results of Disintegration Time

Formula	Disintegration time mean in <i>petri dish method</i> $\pm$ SD	Disintegration time mean in <i>slide frame method</i> $\pm$ SD
FC1	144.76 $\pm$ 10.25	11.33 $\pm$ 1.22
FC2	145.06 $\pm$ 11.42	12.24 $\pm$ 0.87
FD1	19.94 $\pm$ 1.87	4.38 $\pm$ 1.19
FD2	25.03 $\pm$ 2.41	5.45 $\pm$ 0.39
FE1	59.83 $\pm$ 4.57	6.39 $\pm$ 0.42
FE2	49.52 $\pm$ 6.64	6.00 $\pm$ 0.79
Comparison	58.15 $\pm$ 4.42	42.33 $\pm$ 1.67

Note: Repetition (n) = 3

FC1 = HPMC K4M 2% + glycerin 10% of the polymer

FC2 = HPMC K4M 2% + glycerin 30% of the polymer

FD1 = HPMC K4M 2% + PEG 400 10% of the polymer

FD2 = HPMC K4M 2% + PEG 400 30% of the polymer

FE1 = HPMC K4M 2% + PG 10% of the polymer

FE2 = HPMC K4M 2% + PG 30% of the polymer

4. CONCLUSION

The polymer that produced red ginger extract ODF that met the requirements was HPMC K4M with a concentration of 2%. The plasticizer chosen was PEG 400 with a concentration of 30% of the polymer.

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Author Contribution

Febriyenti: Concepts, design, definition of intellectual content, data analysis, manuscripts review, guarantor.

Rizki Siti Aisyah: Literature search, experimental studies, statistical analysis, manuscript preparation, manuscript editing.

Rahima Intan: Literature search, experimental studies, data analysis, manuscript preparation.

Mursal Azizah: Experimental studies, data acquisition, data analysis, manuscript preparation.

Kumalasari Charrisca Syahyuning: Experimental studies, data acquisition, statistical analysis, manuscript preparation.

Susanti Meri: Concepts, design, definition of intellectual content, data analysis, manuscripts review.

Informed consent

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

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Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Data and materials availability

All data associated with this study are present in the paper.

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