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PROPRANOLOL HYDROCHLORIDE ORALLY DISINTEGRATING FILM (ODF) FORMULATION USING SOLVENT CASTING AND ROLLING METHOD

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ABSTRACT
Propranolol hydrochloride (HCl) is a non-selective beta-blocker that is commonly used to treat hypertension, myocardial infarction, and arrhythmia. Conventional tablet preparations often make it difficult for pediatric, geriatric, or gastrointestinal patients with gastrointestinal disorders. To overcome these problems, propranolol hydrochloride was formulated into an Orally Disintegrating Film (ODF). This thin film-shaped preparation disintegrates in the oral cavity within less than a minute, eliminating the need for water. The purpose of this study is to formulate propranolol hydrochloride into ODF using the solvent casting method and rolling method. In the solvent casting method, HPMC E3 is used as the polymer, and three types of plasticizers (glycerin, propylene glycol (PG), and polyethylene glycol (PEG) 400 were employed at two concentrations. The best formula using PEG 400 (F5) produces a transparent, homogeneous, dry film in 72 hours and with a disintegration time of 46.03 ± 0.57 seconds. Content uniformity was 95.38 ± 1.95 (AV = 7.79). The rolling method was developed to speed up the drying process and increase production. The best formula R3 using 6 ml of distilled water produces a transparent, homogeneous, quick-drying film (12 hours), has a disintegration time of 36.00 ± 1.00 seconds, and content uniformity was 99.44% (AV = 13.29).

KEYWORDS: Orally Disintegrating Film, Propranolol Hydrochloride, Solvent Casting Method, Rolling Method.

INTRODUCTION
Oral administration of drugs using solid preparations is the most common method in therapy due to its ease of use, good stability, efficient production process, and ease of storage.[1][2] However, in groups of patients with certain conditions, such as children (pediatrics), the elderly (geriatrics), and patients with impaired gastrointestinal function, they often have difficulty swallowing solid preparations. This can affect patient adherence as well as decrease the effectiveness of treatment, especially in drugs that require rapid onset of action, such as propranolol hydrochloride.[3],[4]

Propranolol hydrochloride is a non-selective β-blocker class drug used in the treatment of cardiovascular diseases such as angina, hypertension, and arrhythmias.[5] Propranolol hydrochloride is generally available in conventional tablet form with doses of 10–40 mg. However, in certain clinical conditions that require quick effects, the tablet form has limitations, such as slower dissolution times and difficulty in consumption by certain patients.

To overcome these problems, an alternative drug delivery system was developed in the form of an Orally Disintegrating Film (ODF). ODF is a thin-film preparation that dissolves easily in the oral cavity without the help of water and can disintegrate in less than a minute. The advantages of ODF include ease of use, convenience for patients with dysphagia, as well as the potential to accelerate the onset of drug action through rapid disintegration and efficient release of active substances.[6]

In this study, propranolol hydrochloride was formulated into ODF using HPMC E3 as a polymer, glycerin, propylene glycol (PG), or polyethylene glycol (PEG) 400 as plasticizers, methyl paraben as a preservative, sorbitol as a sweetener in the solvent casting method, and stevioside as a sweetener in the rolling method. Stevioside is chosen as a sweetener on the rolling method because it has a sweetness level 250–300 times higher than sucrose, it could be used in small amounts, and prevents crystallization in the film.[7]

The ODF could be prepared using various methods, including the solvent casting and the rolling method. The solvent casting method has the advantage of a simple production process and can be used for small-scale production.[8]

However, this method has several drawbacks, namely long drying times and limited production capacity per mold. It makes this method less efficient in large-scale production and risks producing variations in the mold. While the rolling method has the advantage of a more even distribution of the mass of the preparation using a roller and produces a film that dries quickly, uniformly, and in larger quantities.[9]

This study aims to formulate propranolol hydrochloride into ODF using the solvent casting method and rolling method. The results of the research are expected to contribute to the development of oral drug delivery technology that is more effective, efficient, and convenient to use, especially for patients with special needs or in emergency conditions.

MATERIALS AND METHODS

Materials

The ingredient used in this study is propranolol hydrochloride donated by PT. Dexa Medica, Indonesia. Hydroxypropyl methylcellulose (HPMC) E3 was provided by PT. Metiska Farma, Indonesia. Methyl paraben, glycerin, propylene glycol (PG), polyethylene glycol (PEG) 400, ethanol, phosphate buffer, and distilled water were bought from Baratachem, Indonesia. Sorbitol and stevioside were obtained from PT. Tatarasa Primatama, Tangerang. Filter paper was obtained from Whatman, Indonesia.

Methods

Propranolol hydrochloride ODF Preparation

Formulation

Propranolol hydrochloride ODF with size 2 cm x 2 cm contains 10 mg of propranolol hydrochloride. As a mold, a Petri dish with a diameter of 9.1 cm, an area of 65.065 cm^2 was used. One mold could produce 16.27 propranolol hydrochloride ODF. So propranolol hydrochloride in one mold was 162.662 mg ~ 163 mg.[10] The complete composition of the propranolol hydrochloride ODF formula could be seen in Table 1.

Table 1: Formula propranolol hydrochloride ODF using the solvent casting method (for one mold).

Ingredient	F1	F2	F3	F4	F5	F6
Propranolol HCl (mg)	163	163	163	163	163	163
HPMC E3 (mg)	600	600	600	600	600	600
Glycerin (mg)	60	180	-	-	-	-
PG (mg)	-	-	60	180	-	-
PEG 400 (mg)	-	-	-	-	60	180
Sorbitol (mg)	300	300	300	300	300	300
Methyl paraben (mg)	1	1	1	1	1	1
Distilled water (g) up to	10	10	10	10	10	10

Solvent casting method

In the solvent casting method, propranolol hydrochloride and sorbitol were dissolved in distilled water, and then the polymers were developed using the solution. Methyl paraben was dissolved with a plasticizer and then added to the polymer solution. The mixture was then left at room temperature to remove any air bubbles. Once the air bubbles were gone, the film was poured into a mold and dried at room temperature. Once dry, the film was carefully removed from the mold and cut to a size of 2 cm x 2 cm.

Rolling method

In the rolling method, stevioside was used as a sweetener because stevioside has a sweet taste 250-300 times sweeter than sucrose. Stevioside can be used in small amounts and does not cause crystallization. The plasticizer used in this rolling method was the best plasticizer resulting from the solvent casting method. The complete composition of the propranolol hydrochloride ODF formula by the rolling method could be seen in Table 2. One batch was 3 molds.

Table 2: Formula propranolol hydrochloride ODF using the rolling method (for 3 molds).

Ingredient	R1	R2	R3	R4
Propranolol hydrochloride (mg)	489	489	489	489
HPMC E3 (mg)	1800	1800	1800	1800
PEG 400 (mg)	180	180	180	180
Stevioside (mg)	450	450	450	450
Methyl paraben (mg)	3	3	3	3
Distilled Water (g)	16.5	11.25	6	3

Propranolol hydrochloride ODF was made using the rolling method. The apparatus used was a modified roller (Figure 1).

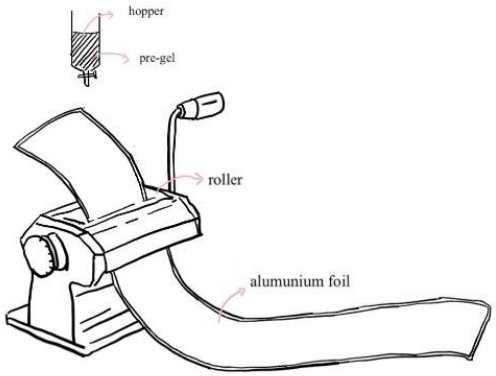

Figure 1: Illustration of the modified roller apparatus.

The parameter studied was the amount of water used in the formula. If the solvent casting method used approximately 9 g of distilled water (equivalent to 18 g for 3 molds), then the rolling method used several variations in the amount of distilled water, as shown in Table 2. ODF pre-gel was produced by dispersing HPMC E3 and methyl paraben in PEG 400, as mass 1. Propranolol hydrochloride and stevioside were dissolved in distilled water, as mass 2. Furthermore, mass 1 and mass 2 were mixed, homogenized, and left to remove air bubbles. The pre-gel was then molded using a roller apparatus with an aluminum foil as a container with a size of 13.5 cm x 14.46 cm, that equal to the area of three Petri dishes. The film formed was dried at room temperature. Once dry, ODF was cut to a size of 2 cm x 2 cm.

Evaluation of Propranolol Hydrochloride ODF Preparations

a. pH Measurement Pre-gel Propranolol Hydrochloride ODF

The pH of the pre-gel was measured using a calibrated pH meter. The electrode pH-meter was dipped into the pre-gel and allowed to wait until the pH was constant.[10][11]

b. Organoleptic

Organoleptic testing was carried out through visual observation. Test parameters were homogeneity, color, texture, and ease of handling.[12]

c. ODF Moisture Content

ODF moisture content is measured using a Moisture Balance at 105°C. This apparatus will display the measurement results.[13]

d. ODF Weight and Thickness Measurement

ODF weight measurement was performed by randomly weighing six ODFs on each formula. The ODF weight is accepted when no ODF deviates significantly from the average weight. While the ODF thickness measurement was carried out using a digital micrometer on 3 parts of the ODF. The measurement results are averaged, and the standard deviation is calculated with an acceptance of less than 5%.[10]

e. Disintegration Time

An ODF should disintegrate in not more than 60 seconds. Disintegration time was carried out using the slide frame method. One ODF sheet in size 2 cm x 2 cm clamped with tweezers. One drop of distilled water was dropped over the ODF, and the time a hole formed on the ODF was determined.[10]

f. Expanding Power

Expanding power measurement was carried out by soaking ODF in 15 ml of phosphate buffer solution for 15 seconds and repeating until a constant weight was obtained.[11]

$$\text{Expanding Power (\%)} = \frac{Wt - Wo}{Wo} \text{ x } 100\%$$

Whereas: Wt: ODF weighs at time t; W0: ODF weight at time 0

g. Content uniformity test

ODF was dissolved in 70% ethanol until a concentration of 10µg/ml was obtained. Measured 288 nm and 253 nm wavelength absorbents with a UV-Vis spectrophotometer.[11]

RESULT AND DISCUSSION

The evaluation results of propranolol hydrochloride ODF prepared using the solvent casting method are shown in Table 3. F1 and F3 were brittle because the amount and type of plasticizer used were not suitable for producing the film form. F2, F4, and F6 were greasy due to the excessive amount of plasticizer used. Therefore, only F5 was film formed. The film was formed within 72 hours.

Table 3: Results of evaluation of propranolol hydrochloride ODF (solvent casting method).

Parameters	Results	Requirement	Conclusion
Organoleptic	F1=brittle, film not formed	Film-formed, homogeneous, transparent, easy to remove from mold.[10]	Not eligible
	F2= greasy, sticky, film-formed, difficult to remove from the mold		Not qualify
	F3=brittle, film-formed, non-removable from mold		Not eligible
	F4= greasy, film-formed, easy to remove from the mold		Not qualify
	F5= film-formed, transparent, easy to remove from the mold		Qualify

	F6= greasy, film-formed, easy to remove from the mold		Not qualify
Weight uniformity (g)	F2 = 0.075 ± 0.004	The weight of each film does not deviate significantly from the average weight of the film.[10]	All formulas qualify
	F4 = 0.069 ± 0.004		
	F5 = 0.077 ± 0.001		
	F6 = 0.082 ± 0.008		
Thickness uniformity (mm)	F4 = 0.069 ± 0.004	0.005-0.200 mm[14]	All formulas qualify
	F5 = 0.077 ± 0.001		
	F6 = 0.082 ± 0.008		
	F6 = 0.181 ± 0.009		
pH of the surface of the preparation	F2 = 7.15 ± 0.14	The surface pH of the preparation is close to neutral.[10]	All formulas qualify
	F4 = 7.12 ± 0.07		
	F5 = 7.10 ± 0.09		
	F6 = 7.15 ± 0.10		
Moisture content (%)	F2 = 8.82 ± 0.66	The smaller the moisture content of the film, the better the stability of the film.[10]	F2, F4, and F5 are qualified. F6 is not qualified
	F4 = 5.81 ± 0.58		
	F5 = 7.35 ± 0.38		
	F6 = 14.12 ± 0.14		
Expandable power (%)	F2 = 149.28 ± 39.44	The expanding power of the film is getting better the bigger.[10]	All formulas qualify
	F4 = 179.18 ± 31.62		
	F5 = 138.34 ± 17.19		
	F6 = 116.20 ± 18.77		
Disintegration time (s)	F2 = 60.07 ± 2.35	< 60 seconds.[10]	All formulas qualify
	F4 = 62.85 ± 2.69		
	F5 = 46.03 ± 0.57		
	F6 = 51.96 ± 3.64		
Content uniformity (%)	F2 = 93.40 ± 3.13 (AV = 12.62)	Rates in the range of 90 - 110% with an acceptance value (AV) < 15.[10]	All formulas qualify
	F4 = 90.79 ± 2.57 (AV = 13.87)		
	F5 = 95.38 ± 1.95 (AV = 7.79)		
	F6 = 96.21 ± 2.26 (AV = 7.72)		

In the rolling method, propranolol hydrochloride ODF was prepared based on the F5 composition. One batch was equal to three molds. The evaluation results of propranolol hydrochloride ODF prepared using the rolling method are shown in Table 4. R1 and R2 could not be printed with a roller because the pre-gel was too thin. A dilute pre-gel could not be printed using a roller. R3 and R4 could be printed and film formed. R4 produced inhomogeneous and opaque films due to the viscous pre-gel. This occurred due to the water used in the formula being insufficient to expand HPMC E3 and dissolve propranolol hydrochloride. Therefore, only R3 produces films that meet the requirements.

Table 4: Results of evaluation of propranolol hydrochloride ODF (rolling method).

Parameters	Results	Requirement	Conclusion
Pre-gel pH	R1= 6.98 ± 0.02	The surface pH of the preparation is close to neutral.[10][15]	Qualify
	R2= 7.17 ± 0.01		Qualify
	R3= 7.20 ± 0.02		Qualify
	R4= 7.56 ± 0.01		Qualify
Organoleptic	R1= could not be printed, film not formed	Film-formed, homogeneous, transparent, easy to remove from print, and dry in 12 hours.[10]	Not eligible
	R2= could not be printed, film not formed		Not eligible
	R3= film-formed, homogeneous, transparent, easy to remove from the mold, and dry within 12 hours		Qualify
	R4= film-formed, not homogeneous, opaque, easy to remove from mold, dry within 12 hours		Not eligible
Weight uniformity (g)	R3=0.059± 0.001	The weight of each film does not deviate significantly from the average weight of the	Qualify
	R4=0.080± 0.010		Not eligible

		film.[10]	
Thickness uniformity (mm)	R3= 0.175 ± 0.005	0.005-0.200 mm.[14]	Qualify
	R4= 0.217 ± 0.046		Not eligible
Disintegration time (seconds)	R3 = 36.00 ± 1.00	< 60 seconds.[10]	Qualify
	R4 = 36.00 ± 32.04		Qualify
Expandable power (%)	R3= 94.90%± 0.40	The expanding power of the film is getting better the bigger.[10]	Qualify
	R4= 32.61% ± 11.20		Qualify
Moisture content (%)	R3= 7.21 ± 0.02	< 10%.[10]	Qualify
	R4=7.93 ± 0.25		Qualify

Based on the results of the evaluation carried out, ODF produced using the rolling method dries faster than ODF produced using the solvent casting method. ODF produced using the rolling method dried within 12 hours, while ODF produced using the solvent casting method dried within 72 hours.

Evaluation of film weight and thickness is important to see the uniformity of the weight and thickness of the preparation because this evaluation has a direct effect on the accuracy of the dosage of the preparation. The average results of the ODF weight and thickness evaluation can be seen in Tables 3 and 4. The weight and thickness of the film can be influenced by various factors, including the amount of ingredients/concentrations used and the molecular weight of the raw material.[16] In the solvent casting of F2, F4, and F6 at the same plasticizer concentration, the weight and thickness of the film experience significant differences. This is due to the difference in molecular weight of each plasticizer.[4] PEG 400 has the largest molecular weight of 380-420; glycerin has a molecular weight of 92.09; and PG has the smallest molecular weight of 76.10. The molecular weight is directly proportional to the weight of the film; the greater the molecular weight of the raw material, the greater the weight of the film will increase.[16]

Meanwhile, the results of the uniformity of the weight and thickness test in the rolling method could be seen in Table 4. The test was only performed on R3 and R4 because R1 and R2 could not be printed. In the R3 weight measurement, there was no significant deviation on average. The measurement results meet the criteria that are between 0.005-0.200 mm.[14] While R4 had a thickness that did not meet the requirement due to the film being inhomogeneous.

The moisture content of the film is one of the important evaluations for film preparations. The moisture content can affect the mechanical properties of the preparation, such as stretching, adhesion, as well as chemical properties, such as dissolution and dissolution time. A small percentage of moisture content can affect the stability of the film in storage.[17,18]

Evaluation of the moisture content of propranolol hydrochloride ODF preparations solvent casting method provides the largest moisture content results in a row, which are F6, F2, F5, and F4. Each of the plasticizers provides a significant difference in the moisture content of the film. This is because PEG 400 has more hydrophilic groups compared to glycerin and PG; therefore, PEG 400 has greater water-binding ability.[19] In F5 and F6, with the use of the same type of plasticizer, PEG 400, it gives very different results. According to the research conducted by Fridayanti (2010) that the higher the concentration of PEG 400 used, the moisture content of the film will increase.[20] The rolling method at R3 and R4 was obtained from the results of the evaluation of the moisture content that met the criteria (less than 10%).

Expanding power has an important role in the release of drugs in the body.[21] The ability of propranolol hydrochloride ODF to expand can be seen in Tables 3 and 4. In the solvent casting method, the ODF experienced the largest expansion power in the order were F4, F2, F5, and F6. In this formulation, the difference in plasticizer affects the polymer's ability to undergo hydration. The PEG 400 plasticizer provides less expanding power than other plasticizers. This is because polymers using PEG 400 plasticizers experience greater hydration during the formulation process, so that in the expansion power test, the free space in the polymer has decreased.

In the rolling method, R3 had more expanding power than R4 due to the HPMC E3, which has expanded perfectly, so that the water absorption is higher than F4. Whereas in F4, HPMC E3 does not expand perfectly, so the thinner film surface will first absorb water.

European Pharmacopoeia 7.4 (2012) states that ODF preparations must disintegrate quickly when placed in the mouth, but the maximum value of the time of disintegration was not stated.[22] Although there are no official guidelines for the ODF disintegration time, previous studies have stated that ODF is a preparation that dissolves quickly and disintegrates in less than 1 minute.[23–25] This parameter becomes the main characteristic of ODF preparation. All formulas met the requirement.

Content uniformity is declared eligible when the average of content in the range of 90 -110% and the acceptance value (AV) is less than.[26] In the rolling method, R3 has content uniformity of 99.44% (AV = 13.29). According to the Pharmacopoeia Indonesia edition V, the content

uniformity of propranolol hydrochloride ODF had met the requirements.[26]

CONCLUSION

The solvent casting and rolling method could produce propranolol hydrochloride ODF. The drying time in the solvent casting method is 72 hours, while in the rolling method is 12 hours. The rolling method could produce more ODF (3 mold) than the solvent casting method (1 mold).

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