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Preparation And Characterization Of Propranolol Hidrocloride Buccal Mucoadhesive Tablet

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Abstract. Propranolol HCl is antihypertensive drug which have low bioavailability (<50%) and short (2-6 hours) elimination half-life. Those problems can be solved by making slow release tablet preparations such us buccal mucoadhesive. Buccal mucoadhesive tablet for the treatment of hypertension propanolol hydrochloride prepared by polymers combination and other excipients. The combination of polymers may affect the delivery of buccal mucoadhesive drugs that can provide controlled release dosage and increase its bioavailability. The purpose of this study to characterize the effect of Carbopol®-HPMC (Hydroxypropyl Methylcellulose) and Carbopol®-CMC Na (Sodium Carboxymethyl Cellulose) as buccal mucoadhesive polymer using direct compression technique. The tablets were evaluated for flow rate and the angle of repose, homogeneity, hardness, friability, uniformity of content, mucoadhesive strength, swelling index, surface pH, propranolol hydrochloride release and dissolution efficiency (DE_{480}). The formula that using the combination of polymer Carbopol® 940P and CMC Na (55:70 mg) was able to provide the best buccal mucoadhesive strength response value. While the formula that using a combination of polymer Carbopol® 940P and HPMC (30:20 mg) has the best DE_{480} value.

Keywords: Propranolol HCl, Buccal mucoadhesive, Polymer, Buccal mucoadhesive strength, DE_{480} value

1. Introduction

Hypertension is a condition of systolic blood pressure more than 140 mmHg and diastolic pressure more than 90 mmHg. It can increase the risk of complications such as heart disease, congestive heart failure, stroke, visual impairment and kidney disease [1]. One of the commonly used antihypertensive drugs is Propranolol Hydrochloride, which acts on non-selective β receptors by inhibiting the adrenergic stimulant response. Propranolol HCl well absorbed in the gastrointestinal tract (>90%), with low bioavailability (<50%) and have short (2-6 hours) elimination half-life [2]. Those problems can be solved by making slow release tablet preparations with a mucoadhesive delivery system, such as buccal mucoadhesive to maintain a longer duration in plasma and the effective absorption site of Propranolol HCl [3]. The critical aspect for buccal mucoadhesive preparations is selecting the properly polymer. In this study, the preparation used a direct compression with the combination of Carbopol® and HPMC (hydroxypropyl methylcellulose) and also Carbopol® with CMC Na (sodium carboxymethylcellulose) as the polymers.

2. Methodology

Instruments that used in this research were analytical balance (Adventure Ohaus), mortar, stamp, flow tester (Pharmeq), single punch tablet (Healthy, China), stoke-monsanto hardness tester (Pharmeq), friability tester (GX4, Pharmeq), dissolution tester (Pharmeq Dissolution Test 2007), pH meter (Hana), Spectrophotometer (Genesys 10S UV-Vis Spectrophotometer, USA), cuvette, buccal mucoadhesive test apparatus (modified), glass tools and software design expert 8.0.6 as a data processing

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program. While the materials were ethanol, monobasic potassium phosphate, sodium hydroxide, aquadest, goat buccal mucosa, and also the main materials for making the tablets (Table 1).

Table 1. Slow-release formulations containing Propranolol HCl

Materials and the Functions	Amount (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Propranolol HCl (active ingredient)	92.4	92.4	92.4	92.4	92.4	92.4	92.4	92.4
Carbopol® 940P (mucoadhesive polymer)	5	30	5	30	25	55	25	55
HPMC K4M (mucoadhesive polymer)	20	20	100	100	-	-	-	-
CMC Na (mucoadhesive polymer)	-	-	-	-	70	70	100	100
Mg stearate 2% (lubricant)	6	6	6	6	6	6	6	6
Ca phosphate dibasic (diluent)	176.6	151.6	96.6	71.6	106.6	76.6	76.6	46.6
Total tablet weight	300	300	300	300	300	300	300	300

The buccal mucoadhesive tablet was prepared by mixing Propranolol HCl, HPMC, CMC Na, Carbopol®, Calcium Phosphate according to the formulation in Table 1. Then added Mg Stearate until homogenous, evaluated the powder flowability and homogeneity before doing the compression.

2.1 Flowability Testing

Used the funnel method, by inserting 100 g of powders in a closed funnel, then recording the time when all of the powders had passed, measured the height (h) and the radius (r) of dropped powders. Then calculated the flow rate and the angle of repose [4].

$$\text{Flow rate} = \frac{mass\ (gram)}{time} \qquad (1)$$

$$\text{Angle of repose } (\alpha) = tan^{-1}\frac{height\ (h)}{radius\ (r)} \qquad (2)$$

2.2 Homogeneity Testing

Determine the maximum wavelength by dissolving 50 mg of Propranolol HCl in 50 ml methanol to obtained 1000 ppm standard solution, then diluted to be 10 ppm. Measured at 200-400 nm wavelength. Preparation the standard solution of Propranolol HCl in 5 ppm, 10 ppm, 15 ppm, 20 ppm, 25 ppm, 30 ppm, 40 ppm, and 50 ppm concentrations at a predetermined maximum wavelength and made the standard curve.

Homogeneity was determined by dissolving the powders that containing 92.4 mg Propranolol HCl in 20 ml aquadest and added methanol until 100 ml, filtered it with Whatman paper. Piped 10 ml and given methanol ad 50 ml, then piped 1 ml and added to be 10 ml with methanol (5 replications).

2.3 Hardness Testing

Used 10 tablets, each tablet placed on the hardness tester with an upright position, then the screw rotated until tablet breaks.

2.4 Friability Testing

Used 20 tablets, then weighed the tablets (W1) and entered in the friability tester with 25 rpm for 4 minutes. Then cleaned and weighed the tablet again (W2) (3 replications) [4].

$$\%\ \text{Friability} = \frac{W_1 - W_2}{W_1} \times 100\% \qquad (3)$$

2.5 Content Uniformity Testing

To measure the maximum wavelength and the standard curve is same as on the determination of Propranolol HCl content in the powder. Uniformity of Propranolol HCl tablets is determined by using 20 tablets that equivalent to 92.4 mg. The next step is also like as determining powder homogeneity.

2.6 Swelling Test

Tablet was weighed (W1) and placed on a different petri dish with 5 mL phosphate buffer solution (pH 6.8). Moved excess water on the surface with filter paper horary for 8 hours. Weighed again the tablet (W2) and determined the swelling index (SI) [5].

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100\ \% \qquad (4)$$

2.7Measuring The Surface pH of Tablet

Buccal tablets laid on the surface of 1 ml of CO_2-free distilled water for 2 hours at room temperature, then measuring the surface pH of the tablet for 1 minute.

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2.8Tests Measuring Mucoadhesive Strength

Tablets were put on the goat buccal mucous membrane that has been separated from the fat and free tissue, also has been washed with aquadest and phosphate buffer pH 6.8 at 37°C. Then a constant load of 5 g was given for 5 minutes. Mucoadhesive buccal strength is measured according to the weight of the load that can be release tablet from the membrane.

2.9Propranolol HCl Release Test

Flask dissolved on an apparatus 2 dissolution test (solved paddle) containing 900 ml phosphate buffer pH 6.8 and Propranolol HCl is using 50 rpm at 37 ± 0.5ºC. Sampling was conducted at 15, 30, 45, 60, 120, 240, 360 and 480 min by taking 5 ml of phosphate buffer solution and 5 ml of new phosphate buffer solution was returned. The sample solution was filtered with 0.2 µm Whatman filter paper and then analyzed by UV spectrophotometry at the maximum wavelength.

3. Result

3.1 Mixed Powders

3.1.1 Flow rate and the angle of repose

The powder mixture of all formulas has a poor flow character which an angle of repose >40º and high cohesive properties, so it can't flow freely [4]. The flow rate of a good powder mixture is 10 grams/sec which an angle of repose not more than 40º [6].

3.1.2 Content of Propranolol HCl in powder mixture

The powder mixture of all formulas has CV value <6%, so overall it is said to be homogeneous because fulfill the requirements of Farmakope Indonesia IV (Table 2).

Table 2. Propranolol HCl homogeneity testing in the powder mixture

Formula	Average of % *Recovery* ± SD	CV (%)	Formula	Average of % *Recovery* ± SD	CV (%)
F1	97.304 ± 0.725	0.745	F5	95.904 ± 1.310	1.366
F2	96.025 ± 0.374	0.389	F6	91.852 ± 1.056	1.150
F3	96.573 ± 1.046	1.084	F7	92.019 ± 1.085	1.179
F4	97.623 ± 0.852	0.870	F8	93.240 ± 2.795	2.998

3.2 Propranolol HCl Tablets

3.2.1 Tablet compression process

Tablets are compressed one by one using single-punch tablet press because the powder mixture has a poor flow character.

3.2.2 Physical properties of tablets

Material properties and compacted can significantly affect tableting performance to satisfy the range of hardness control in 4-8 kg. While the requirement of frailty or allowable weight loss is ≤1% [4]. The results of the hardness testing and the fragility of the tablets indicate that all of the formula satisfy the requirements (Table 3).

3.2.3 Content uniformity testing

All of the formulas satisfy the requirements of uniformity content in according to USP (Propranolol HCl not less than 90% and not more than 110%) and compatible with relative standard deviation by Farmakope Indonesia IV that <6% (Table 3).

3.2.4 Buccal mucoadhesive strength

The range of buccal mucoadhesive strength that strong enough to perceived in the buccal layer is 20-40 grams. Which formula that satisfy the requirements is F2, F3, F6, and F8 (Table 3).

3.2.5 Surface pH testing

Carbopol® as polymer has a pH range between 2.5-3.0, HPMC has 5.5-8.0, and CMC Na has 4.5-6 [7]. While the pH range of the desired buccal tablet that doesn't irritate the buccal mucosa is 5.5-7.0 [8]. The formula that satisfies the requirements range is F1 (Table 3).

3.2.6 Swelling test

Swelling is characteristic that indicated uniformity, controlled drug release, and effective mucoadhesive ability. The desired swelling index is 65% -75% [5]. Formulas that satisfy the requirements are F2 and F3 (Table 3).

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Table 3. Test results of Propranolol HCl tablets

F	Hardness (Kg)	Fragility (%)	Content uniformity (%)	Buccal mucoadhesive strength (g)	Surface pH	Swelling index (%)
1	4.2 ± 0.178	0.961 ± 0.054	100.394 ± 1.522	4.860 ± 0.548	5.47 ± 0.096	45.329 ± 1.505
2	5.4 ± 0.459	0.414 ± 0.034	99.739 ± 1.383	28.860 ± 0.548	3.73 ± 0.091	70.533 ± 2.982
3	5.95 ± 0.158	0.608 ± 0.046	102.019 ± 1.555	24.860 ± 0.548	5.32 ± 0.031	69.662 ± 10.033
4	6.8 ± 0.422	0.394 ± 0.027	99.201 ± 2.405	43.860 ± 0.548	3.82 ± 0.048	78.791 ± 4.302
5	4.6 ± 0.84	0.799 ± 0.020	92.241± 1.603	8.477 ± 1.224	3.958 ± 0.101	241.284 ± 11.003
6	6.25 ± 0.42	0.498 ± 0.014	92.712 ± 2.190	30.877 ± 1.816	3.5 ± 0.02	220.240 ± 5.011
7	4.4 ± 0.51	0.697 ± 0.038	93.462 ± 1.146	13.877 ± 1.341	4.154 ± 0.063	339.866 ± 8.866
8	4.45 ± 0.59	0.678 ± 0.106	93.240 ± 2.290	20.077 ± 3.577	3.664 ± 0.054	301.772 ± 1.841

3.2.7 Propanolol HCL release

Based on Figure 1, the percentage of Propranolol HCl release from the largest to the smallest was F4 <F3 <F8 <F2 <F6 <F1 <F7 <F5.

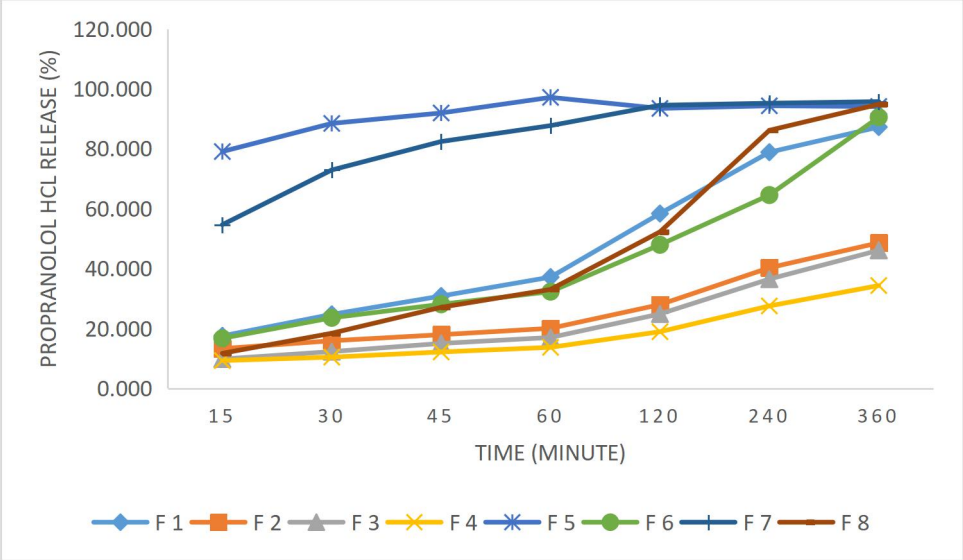

Fig 1. Dissolution profile

3.2.8 Dissolution efficiency (DE)

Dissolution efficiency (DE) indicate the percentage between area under the curve at a certain time (t) with an area that representing 100% dissolution at the same time (t) [9]. DE_{480} that expected on this Propranolol HCl tablet is 45-65%. This range selected to make all of the formulas follow the zero order. The eligible formulas are F2, F3, F4, F6, and F8 (Table 4).

Table 4. Analysis DE_{480}

Formula	DE_{480} (%)	Formula	DE_{480} (%)
F1	66.971	F5	94.667
F2	64.387	F6	63.586
F3	61.113	F7	88.296
F4	62.722	F8	63.468

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3.2.9 The kinetic analysis of dissolution Propranolol HCl release

Based on Table 5 some formulas do not have the greater r-values than r tables. The r value of the table was used as a limit to indicate a good relation between x and y in each equation, so the data was considered linear when the value of r ≥ r table. Then r value was used to decide the determinant coefficient (r^2), that shows the dominant release mechanism. All formulas have the highest determinant coefficient (r^2) value on the Higuchi model kinetics. This indicates that the release of Propranolol HCl from the matrix tablet is dominated by the diffusion mechanism.

Table 5. The kinetic analysis of dissolution Propranolol HCl release

Formula	(r) and (r^2) value			
	r table (n=6)	Zero order kinetics	First-order kinetic	Higuchi kinetic
F1	r = 0.8110	r = 0.9425 r^2 = 0.8882	r = 0.8804 r^2 = 0.7750	r = 0.9845 **r^2 = 0.9693**
F2	r = 0.8110	r = 0.9867 r^2 = 0.9736	r = 0.9515 r^2 = 0.9054	r = 0.9984 **r^2 = 0.9969**
F3	r = 0.8110	r = 0.9928 r^2 = 0.9857	r = 0.9489 r^2 = 0.9004	r = 0.9984 **r^2 = 0.9967**
F4	r = 0.8110	r = 0.9931 r^2 = 0.9862	r = 0.9606 r^2 = 0.9234	r = 0.9973 **r^2 = 0.9947**
F5	r = 0.8110	r = 0.504 r^2 = 0.254	r = 0.500 r^2 = 0.250	r = 0.602 **r^2 = 0.363**
F6	r = 0.8110	r = 0.980 r^2 = 0.960	r = 0.930 r^2 = 0.865	r = 0.994 **r^2 = 0.989**
F7	r = 0.8110	r = 0.681 r^2 = 0.463	r = 0.642 r^2 = 0.412	r = 0.783 **r^2 = 0.614**
F8	r = 0.8110	r = 0.946 r^2 = 0.896	r = 0.872 r^2 = 0.761	r = 0.984 **r^2 = 0.969**

4. Discussion

Calcium phosphate dibasic was used as a filler to give a good compounding property [7]. Then Carbopol® as a polymer can provides sufficient hardness of the tablets and can swell rapidly [10]. The HPMC polymer is characterized as a binder of tablets [7], but in form of the gel layer, it will swell slowly [11]. While CMC Na actually can decrease the tablet hardness and increase the disintegration time [7].

The formula that using Carbopol® and CMC Na (Formula 6) as buccal mucoadhesive polymer has a better buccal mucoadhesive strength response than a combination of Carbopol® with HPMC. While the formula using Carbopol® and HPMC (Formula 2) has a better DE480 value than the combination of Carbopol® with CMC Na.

The mechanism of Carbopol® interactions in buccal mucoadhesive occurs by the hydration of polymers on the surface of the mucus. The hydration causes the relaxation and forms a hydrogen bond with mucin [10]. In addition, the Carbopol® will ionize at the salivary pH into a COO-group and form a secondary bond with the mucin hydrogen bond. This is because Carbopol® swell rapidly and interpenetrates toward the mucous membranes. While the Carbopol® mechanism in inhibiting the rate of Propranolol hydrochloride release by hydration in the outer layer of the tablet and form a gel layer that can be obstacle in releasing the active ingredient [10].

The mechanism of HPMC interaction in the buccal mucoadhesive system occurs by hydrogen bonding. HPMC has a hydroxyl group (-OH) that will interact with the mucin mucosa and the presence of water. HPMC have slow hydration. Additionally, HPMC is the hydrophilic polymer that swells slowly to form a gel that will give the bond strength of the mucosa in the long period, so it also serves as a drug release control membrane [11].

The mechanism of CMC Na interaction in the buccal mucoadhesive system occurs by hydrogen bonding. CMC Na has a group of -OH and COO^- which can form by hydrogen bonds with sialic acid, oligosaccharide chains or proteins from mucin [12]. While the mechanism of CMC Na in inhibiting the rate of Propranolol hydrochloride release by ionization the carboxylic groups. This ionization can increase the tablet expandability which can form a gel layer. Increased the viscosity of gel layer around the tablet is proportional with increased concentration of hydrogel (CMC Na) which can keep the rate of drug release [13].

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5. Conclusions

The results of this study indicate that the formula using a combination of polymer Carbopol® 940P and CMC Na (55:70 mg) is able to provide the best buccal mucoadhesive strength response. While the formula using a combination of polymer Carbopol® 940P and HPMC (30:20 mg) has the best DE480 value.

In vivo testing is needed to further investigate the strength of buccal mucoadhesive and the dissolution profiles of Propranolol HCl tablet.

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