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Optimization of hydroxypropyl methylcellulose and sodium carboxymethyl cellulose in buccal film salbutamol sulphate

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Abstract.
Context: Salbutamol sulphate has first pass metabolism in liver and degrade in the colon. That problem could solve by buccal mucoadhesive delivery system. **Aims**: This study was to determine the effect of using HPMC and SCMC polymers on buccal mucoadhessive preparations. **Settings and Design**: The optimization was using simplex lattice design with proportion HPMC and SCMC in formula F1 (20:5), F2 (12.5:12.5), and F3 (5:20). **Methods and Material**: Production of the buccal film was by casting solvent and then optimized in the response of swelling index test, mucoadhesive strength test, and *in vitro* mucoadhesive residence time. Characterization of optimum formula with FTIR test. **Statistical analysis used**: ANOVA ($p < 0.05$) in Simplex lattice by Design Expert version 11.0.1 **Results**: The result of swelling index test showed F1 < F2 < F3; mucoadhesive strength test showed F1 < F3 < F2; and *in vitro* residence time test showed F1 < F3 < F2. The optimum formula found in a proportion of HPMC and SCMC (11.346; 13.654) with swelling index 3.985; a mucoadhesive strength of 36.1 gF; and in vitro residence time of 300 min. The results of FTIR analysis showed that there was no chemical interaction that could change the salbutamol sulphate functional group as the active ingredient that related to therapeutic effect. **Conclusions**: The combination of HPMC and SCMC could give the optimum response in the buccal film preparations.

Keywords: Bronchodilator, mucoadhesive, treatment of asthma

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Introduction

Salbutamol sulphate was a bronchodilator that indicated for the treatment of asthma, bronchospasm, and chronic obstructive pulmonary diseases such as chronic bronchitis and emphysema[1]. This drug was widely used because it was the safest and most effective bronchodilator. This drug was not suitable given orally because it experiences first–pass metabolism in the liver and degenerates in the colon[2]. This caused a low bioavailability of drugs which was only 40 % with a half–life of 4 h to 6 h when used orally[1],[2].

The right drug delivery system to overcome the problem of first–pass metabolism was the transmucosal route. The transmucosal route has the advantage of being able to deliver the drug directly to the systemic circulation by utilizing the sublingual mucosa and buccal mucosa as a place to absorb the drug with two different therapeutic purposes[3]. The form of buccal film preparation has the advantage of being able to avoid first–pass metabolism, the drug directly enters the systemic circulation, can avoid degeneration, and easily stopped if an unwanted reaction occurs[4]. Buccal mucoadhesive was a drug delivery system by placing the drug on the gum or on the cheek[5].

The polymer functions to control the speed of drug release from the preparation[6]. The use of mucoadhesive polymers in the formulation of buccal film preparations was highly recommended because contact between the film and buccal mucosa can occur as desired buccal delivery. The polymers used are Hydroxypropyl Methylcellulose (HPMC) and Sodium Carboxymethyl Cellulose (SCMC). Both of these polymers have good mucoadhesive ability and film forming agent[7]. HPMC has very good acceptability and is a polymer who can control the speed of drug release[8]. SCMC in buccal mucoadhesive preparations acts as an excipient that functions to protect product attachment from damage to mucous tissue[9]. HPMC which was used singly produces fragile film characteristics, while SCMC which was used singly produces sticky film characteristics. The use of a combination of HPMC and SCMC produces better characteristics[10].

The evaluation of the preparation was the organoleptic test, folding resistance, weight uniformity, thickness uniformity, dosage surface pH, swelling index, drug contents in the preparation, Fourier Tansform Infrared Spectroscopy (FTIR), mucoadhesive strength, and in vitro mucoadhesive residence time.

In this study, optimization of the combination of HPMC and SCMC polymers as the forming material for salbutamol sulphate buccal film with the design simplex lattice method. The results of this study were expected to produce buccal film formulas that have characteristics that good requirements.

Materials and Methods

The tools used in this study include: AlpHa Bruker FT–IR Spectrophotometer, TA. XT plus Texture Analyzer, spectrophotometer (Genesys 10S UV–Vis, Thermo Scientific, USA), pH meter (Elmetron CP–502), type dissolution test equipment

paddle (Logan), oven (Memmert, Germany), analytical scales (Adventurer TM Ohaus, USA), hot plate (IKA C–MAG HS 4), stirrer, desiccator (Normax), mortir, stamper, screw micrometer, glass tools, Design Expert software trial version 10.0.1 and software validation method of analysis.

The materials used in this study include: salbutamol sulphate (PT. Phapros, Indonesia), HPMC (PT. BrataChem), SCMC (PT. BrataChem), Propylene Glycol or PG (PT. BrataChem), KH_2PO_4 (PT. BrataChem), NaOH (PT. BrataChem), HCl (PT. BrataChem), Sorbitol, Aquadest, and buccal mucosa of male goats aged ± 1 yr (obtained from slaughterhouses).

Preparation of buccal film

The making of salbutamol sulphate buccal film preparations was carried out by the solvent casting method. The first step was to weigh salbutamol sulphate, HPMC, SCMC, propylene glycol, and sorbitol with compositions according to the formula. Making polymers was by developing HPMC with distilled water, while for SCMC dissolved in hot water. Then stirred until homogeneous and mixed into one then propylene glycol. Salbutamol sulphate dissolved with sorbitol then poured into a polymer mixture. All mixtures stirred until homogeneous using a magnetic stirrer at a speed of 100 rad s^{-1} for 15 min. The mixture was left overnight for a clear and bubble–free solution. The next step was drying use an oven with a temperature of 50 °C for 24 h. The resulting dry film was cut until size 2 cm × 1 cm using a cutter and the sample packed in aluminum foil then stored in a desiccator.

Table 1. The desaign of the buccaal film formula

Composition	**Formula (mg)**		
	1	**2**	**3**
Salbutamol sulphate	144	144	144
HPMC	720	450	180
SCMC	180	450	720
Propilen glycol	1.038	1.038	1.038
Sorbitol	1 490	1 490	1 490
Aquadest	30 mL	30 mL	30 mL

Evaluation of buccal film

Organoleptic test for buccal film salbutamol sulphate dosage forms was carried out by observing the color, smell, taste, shape, and texture of the buccal film. Weight uniformity test of the buccal film was carried out by taking three films randomly from each formula then weighing one by one using analytical scales and then calculated the average value and standard deviation.

The thickness uniformity test of the buccal film was carried out by taking three films randomly from each formula and then measuring the thickness at five

different points (the middle and four corners of the film) using a micrometer, then calculating the average value for each formula[11].

Folding endurance test of buccal film salbutamol sulphate was determined by folding the film repeatedly in the same place up to 300 times or until the film was damaged. Replication three times, the film was good if it has a folding endurance up to 300 times or more[12]. pH surface test for buccal film salbutamol sulphate was prepared by soaking the dosage forms in 5 mL purified water for 1 h. The surface pH of the film was measured using a pH meter and replicated three times. The surface pH value of buccal film dosage forms that not irritating mucosal was in accordance with the range of buccal pH 5.5 to pH 7[13].

Determination of salbutamol sulphate drug content in buccal film dosage forms was carried out by dissolving buccal film in phosphate buffer solution pH 6.8 and observed its absorption using UV–Vis spectrophotometer at the maximum wavelength of salbutamol sulphate which was 276 nm. The experiment was carried out with three replications. Percent active ingredient content in buccal film salbutamol sulphate then calculated using the following equation (1):

% Active ingredient content = (experimental / theoretical results) × 100 % (1)

Requirements ranging from 90 % to 107 % and CV criteria standards less than 5.3 %[14].

Swelling index test was carried out by measuring an initial weight of the film (W0), then a film was allowed to swelling in a petri dish containing phosphate buffer solution pH 6.8. The final weight of the film (Wt) measured at the time interval of 5 min, 10 min, 15 min, 30 min and continues until the weight is constant. The swelling index then calculated using the following Formula (2):

Swelling index (%) = (Wt – W0) (W0 × 100)$^{-1}$[13] (2)

The mucoadhesive strength test in buccal film salbutamol sulphate was carried out with a modified Texture Analyzer, the device was connected to a computer and operated using XTRA Dimension Software. Buccal mucosa tissue of goat washed with phosphate buffer solution pH 6.8, then cut and washed again with a phosphate buffer solution with the same pH[15]. Buccal film salbutamol sulphate was cut to the size of the probe, then placed on the tip of the probe using double tape[16]. Buccal mucosa of goat then attached to the plate with the mucosal position facing out and given a saliva–like liquid. The device was set to provide a force of 500 gF at a speed of 0.5 mm s^{-1} for a 10 s contact time. After that, the probe lifted at a speed of 1 mm s^{-1} to a distance of 10 mm. The device would produce a curve that showed the relationship between time and force required to release the film from the buccal mucous tissue. The curve would be recorded and displayed on a computer screen by producing a value that showed the mucoadhesive strength in units of kilogram–force (kgF). Tests were carried out with three replications[17].

In vitro mucoadhesive residence time test in buccal films salbutamol sulphate was carried out by attaching film on the buccal mucous tissue of goat that previously

rinsed with phosphate buffer pH 6.8. Buccal mucosa tissue of goat placed on the object glass with adhesive then placed on the edge of the beaker glass. Beaker glass filled with 200 mL phosphate buffer solution pH 6.8 and stored at 37 °C ± 0.5 °C, stirring at 50 rad s^{-1} using a magnetic stirrer. *In vitro* mucoadhesive residence time observed for 6 h, measurements were started from the time when buccal film attached until buccal film detached from the buccal mucous tissue of goat.

Determination of optimum formula

Determination of the optimum formula was done by processing swelling index response, mucoadhesive strength, and in vitro residence time of the three formulas that good criteria with the Design Expert trial version 10.0.1. In this study, the desired swelling index criteria were > 2 times the initial weight after 60 min, the criteria for mucoadhesive strength were > 5 gF, and the criteria for residence time were 240 min to 360 min.

Characterization

The FTIR test to determine whether there was an interaction between the active ingredients of salbutamol sulphate and the polymer used. This test used an FTIR spectrophotometer at wave numbers 600 cm^{-1} to 4 000 cm^{-1}. Scanning was carried out on pure salbutamol sulphate and the optimum sample formula for buccal salbutamol sulphate film. The spectra produced by each sample, then compared to see whether there was interaction on the tested formula. If it does not show a significant band shift in the wavelength of salbutamol sulphate, there was no functional group interaction that can affect the therapeutic effect of salbutamol sulphate[18].

Drug release test in buccal film salbutamol sulphate was carried out using paddle type dissolution test equipment. The dissolution medium used was 100 mL phosphate buffer pH 6.8 and the release test was carried out at 37 °C ± 0.5 °C with a stirring speed of 50 rad s^{-1}. The release test was carried out for 5 h by taking 5 mL samples at the 0 min, 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 150 min, 180 min, 210 min, 240 min, 270 min, and 300 min. Amounts of sample volume taken and replaced with a dissolution medium with the same volume at each sampling. Then the samples filtered and analyzed using a UV–Vis spectrophotometer at the maximum wavelength. The amount of drug released at this time interval and the cumulative amount of drug released calculated to determine the drug release profile curve[13].

Statistic analysis

Software Design Expert trial version 10.0.1 and software validation methode of analysis.

Result

Combination composition of HPMC And SCMC based simplex lattice desaign

Table 2. Combination composition of HPMC and SCMC

Komposisi	Formula		
	1	2	3
HPMC (mg)	20	12.5	5
CMC Na (mg)	5	12.5	20

Physical properties evaluation of buccal film salbutamol sulphate

Figure 1. (a) Film F1, (b) Film F2, (c) Film F3

Table 3. Physical ecaluation result of buccal film

Evaluation	F1	F2	F3
Weight Uniformity (mg)	57.5 ± 0.721	53.8 ± 0.850	72.0 ± 1.007
Thickness Uniformity (mg)	0.326 ± 0.005	0.298 ± 0.004	0.338 ± 0.004
Folding Endurance	> 300	> 300	> 300
Surface pH	6.04 ± 0.09	6.39 ± 0.06	6.33 ± 0.01

Data presented as mean ± standard deviation

Determination of drug content in buccal film salbutamol sulphate

Table 4. Drug content determination in buccal film

Formula	Drug Content (%)
F1	97.754 ± 4.97
F2	89.476 ± 2.718
F3	99.001 ± 3.550

Data presented as mean ± CV

Swelling index

Table 5. The result of swelling index test

Formula	Swelling Index
F1	3.522 ± 0.199
F2	3.948 ± 0.168
F3	4.225 ± 0.193

Data presented as mean ± standard deviation

Mucoadhesive strength

Table 6. The result of mucoadhesive strength test

Formula	Mucoadhesive strength (gF)
F1	16.67 ± 0.35
F2	48.7 ± 5.64
F3	25.43 ± 1.16

Data presented as mean ± standard deviation

***In vitro* mucoadhesive residence time**

Table 7. Test result of *in vitro* mucoadhesive residence time

Formula	Residence Time (Min)
F1	276.0 ± 4.58
F2	301.3 ± 5.03
F3	294.7 ± 3.05

Data presented as mean ± standard deviation

Determination of optimum formula

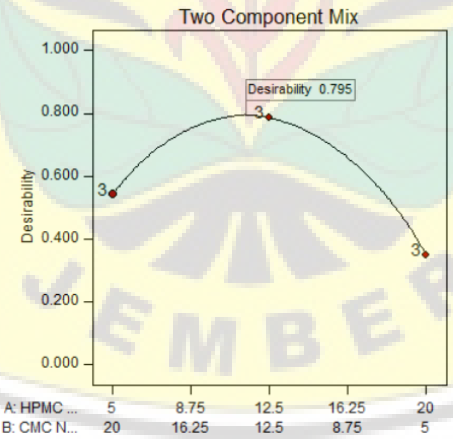

Figure 2. Relationship curve between composition and desirability

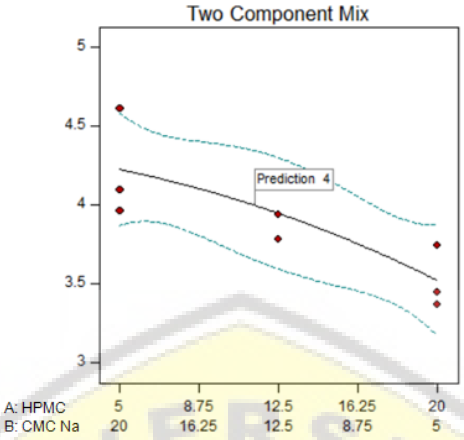

Figure 3. Prediction curve of swelling index in optimum formula

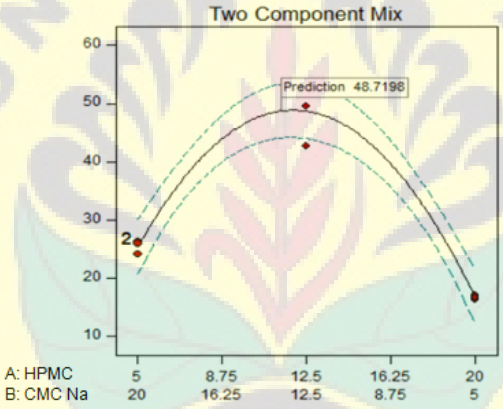

Figure 4. Prediction curve of mucoadhesive strength in optimum formula

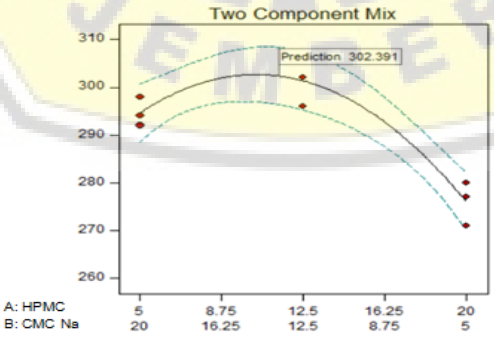

Figure 5. Prediction curve of in vitro residence time in optimum formula

Evaluation of optimum formula

Table 8. Characteristics evaluation in optimum formula of buccal film salbutamol sulphate

Organoleptie	Texture : flexible Ordo : odorless Color : colorless Surface : Smooth, flat, moist Taste : little sweet
Weight uniformity (mg)	66.167 ± 3.419
Thickness uniformity (mm)	0.33
Folding endurance	> 300 ×
Surface pH	6.36 ± 0.085
Drug content (%)	90.221 ± 5.185
Swelling index (t = 60 min)	3.985 ± 0.319
Mucoadhesive strength (gF)	36.1 ± 4.776
Residence time (min)	300 ± 9.539

Characterization

a) FTIR

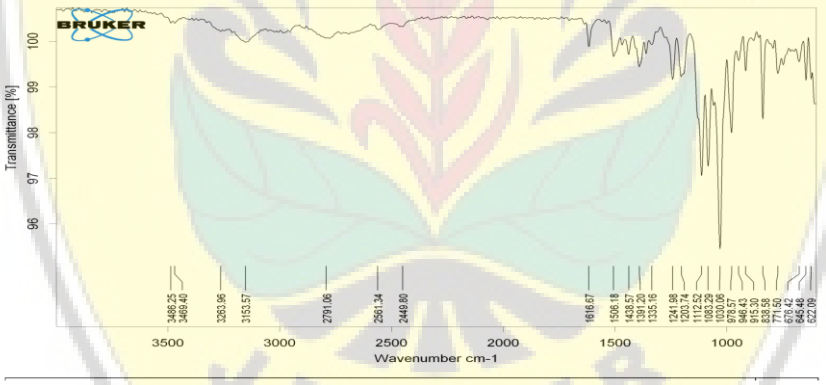

Figure 6. Spectra FTIR of pure salbutamol sulphate

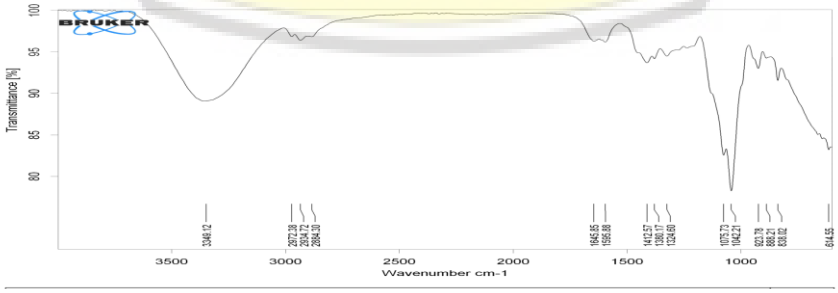

Figure 7. Spectra FTIR of optimum formula of buccal film salbutamol sulphate

Table 10. Interpretation of overlaying pure salbutamol sulphate with each polymer and optimum formula of buccal film salbutamol sulphate FTIR spectra

Functional group	Wave number (cm^{-1})			
	HPMC	CMC Na	Salbutamol sulphate	Buccal film salbutamol sulphate
C = O	1 650.49	–	–	1 645.85
O – H	3 425.45	3 369.80	3 469.40	3 349.12
C – O	1 062.99	1 058.09	1 030.06	1 042.57
C – H	2 911.51	2 850.20	–	2 884.30
C = C	–	–	1 616.67	1 645.85
C – C	–	1 591.51	1 506.18	1 595.88
– NO_2	–	–	1 506.18 and 1 391.20	1 595.88 and 1 380.17
S = O	–	–	1 083.29	1 075.73
C – H	–	–	838.58	838.02

b) Percent drug realease

Table 11. The result of drug release test

Time (min)	(% Drugs release)		
	R1	R2	R3
0	0	0	0
5	1.498	4.095	3.643
10	3.720	15.531	9.880
15	15.156	20.175	12.101
30	21.074	22.871	16.542
45	28.115	32.559	24.651
60	42.422	34.906	30.963
90	45.593	40.230	40.559
120	61.773	47.640	44.951
150	73.059	65.393	55.083
180	78.726	69.688	61.309
210	78.726	77.303	72.046
240	85.818	82.996	75.855
270	90.512	88.814	81.865
300	95.705	93.458	88.458
Mean ± SD	92.540 ± 3.710		
CV	4.009		

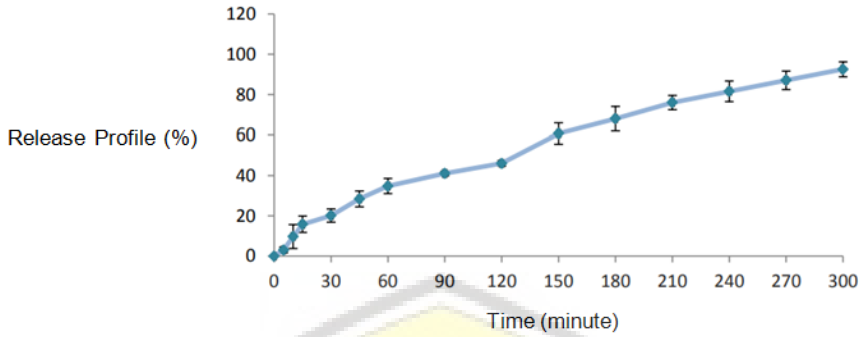

Figure 8. The results of % release profile in optimum formula buccal film salbutamol sulphate

Discussion

The buccal film was made in three formulas with the independent variable in the form of a combination of HPMC and SCMC polymers and the dependent variable was a response from the swelling index test, mucoadhesive strength and in vitro residence time. Preparation of salbutamol sulphate buccal film preparations were carried out by solvent-casting technique. The preparation made with a 9.6 cm diameter mold so that from one sheet the resulting film can be cut into 36 films measuring 2 cm × 1 cm. The composition of HPMC and SCMC used for making buccal film preparations in one mold is a formula for 36 films.

The organoleptic test results of buccal film preparations (Figure 1) showed that the preparations produced had a smooth, flat, but slightly moist surface, the shape of the film was quite thin, flexible, odorless, colorless, and had a slightly sweet taste. Flexible film texture caused by the use of propylene glycol for the purpose of increasing flexibility so that the resulting film has physical characteristics that are not brittle, easy when making preparations from the mold, and also easy when cutting preparations. The surface condition of the film which was slightly damp was also caused by the use of hygroscopic HPMC and SCMC, while the sweet taste comes from sorbitol which was used in the preparation.

The weight uniformity test results (Table 3) showed that the resulting films have uniform weight in one sheet of film ranging from 52.9 mg to 72.9 mg with a small elementary value. The film formed from the dominant SCMC (F3) polymer has a greater weight than the other two formulas (F1 and F2). This was because SCMC has the high swelling ability so that with the same drying time, films with the dominant component of SCMC were more difficult to release water during the drying process. SCMC was also hygroscopic so it can absorb moisture after the film

dried. The difference in film weight will then affect the amount of salbutamol sulphate active ingredient in each film.

The results of testing the uniformity of film thickness (Table 3) showed the thickness of the film for each formula sorted from the thickest are as follows F3 > F1 > F2. F3 films have a slightly higher thickness compared to F1 and F2 because F3 contained large amounts of SCMC. This was related to higher SCMC swelling ability compared to HPMC[6].

The results of folding resistance testing (Table 3) showed that all formulas have a folding resistance of more than 300 times. Factors that affect the resistance of folding film are polymers and plasticizers used in the preparation. The HPMC polymer, when used singly, results in the characteristics of a rigid and slightly brittle film that required the addition of SCMC to increase film flexibility. The film preparations using folding power HPMC polymers increased with the addition of CMC Na[18]. The folding resistance also showed because that the differences in polymer composition and PG plasticizers used in the preparation can produce good film strength and elasticity[17]. Showed films have the ability to withstand the mechanical movements that occur during the used of preparations in the oral cavity.

The surface pH test results (Table 3) showed the pH of the preparation in the range of 5.97 to 6.46. Based on pH measurements carried out on each formula, the pH value produced by the three preparations has met the criteria for the buccal pH range, which was between pH 5.5 to pH 7 or pH that can be tolerated by the oral cavity, which ranges from 5.8 to 7.6[19].

The results of the determination of salbutamol sulphate content showed that salbutamol sulphate gave maximum absorbance at a wavelength of 276 nm which was equal to 0.352. This is consistent with the literature which states that the maximum wavelength of salbutamol sulfate is 276 nm [20]. The measurement results of the standard curve of salbutamol sulphate in a phosphate buffer solution of pH 6.8 produced a linear regression Equation (3):

$$y = 0.00\ 578\ x + (-\ 0.00\ 147) \quad (3)$$

with a correlation coefficient (r) = 0.9 990. The linearity test results showed that the standard curve equation was linear because it has a correlation coefficient > 0.99 with a V × 0 value of 2.074 184 0 % and an Xp value of 9.718 959 0. Xp value to be good if it has a value lower than the smallest concentration analyzed. The range of the average value of percent recovery required for the concentration of active ingredients in the preparation < 100 mg L^{-1} was 90 % to 107 % with CV values < 5.3 %[13]. The result of the drug content test (Table 4) shows that the three formulas good the requirements of the CV value which was less than 5.3 %. Low

levels in the F2 test results can be caused by the loss of active ingredients during the preparation process and when the process of preparation for assay.

The results of the swelling index test (Table 5) showed the swelling index value from the smallest to the largest, namely F1 < F2 < F3. Formulas with a greater composition of SCMC (F2 and F3) produce a higher swelling index value. This was because SCMC has a higher swelling ability compared to HPMC[6]. The swelling index value was then used as an important parameter to predict the mucoadhesive strength produced by the film and percent drug release from the salbutamol sulphate buccal film preparation. The swelling index can increase mucoadhesive strength because water needed in the mucoadhesive process to hydrate the polymer so that it can form a bond with the mucosa. Excessive hydration can be caused a decreased in mucoadhesive strength due to the formation of slippery mucus[23].

Mucoadhesive in vitro strength tests was carried out to determine the ability of the film to attach to buccal tissue so that it does not shift or detach at the time of application and was not swallowed. The greater the force needed, the greater the strength of mucoadhesive[6]. The results of the in vitro Mucoadhesive adhesive test (Table 6) showed F1 < F3 < F2. F2 films with the same composition of HPMC and SCMC have the greatest mucoadhesive strength compared to the other two formulas. HPMC has moderate mucoadhesive properties compared to SCMC which has high mucoadhesive properties, so the combination of HPMC and SCMC with the same composition results in greater mucoadhesive properties compared to the combination of polymers with the dominant component of HPMC or SCMC dominant[6].

The results of the in vitro mucoadhesive residence test (Table 7) showed that F1 < F3 < F2. F2 and F3 have longer residence times compared to F1 because they have a higher SCMC concentration. When viewed from the mucoadhesive strength test performed on all three formulas, the residence time of the three formulas was in accordance with the results of mucoadhesive strength. The higher the strength of the mucoadhesive preparation, the stronger the ability to attach the preparation to the mucosa, resulting in longer residence time. This is related to intensive contact that occurs between polymers and epithelial barriers which allows for an extension of residence time at the absorption site[21].

Determination of the optimum formula was obtained by looking at the contour plot of the swelling index response, mucoadhesive strength, and in vitro residence time so that it would form a composition formula versus desirability curve. A good desirability index value was close to one (Figure 2). The optimum point is shown in Table 8.

Evaluation of the optimum formula [Table 9] showed that the produced salbutamol sulphate buccal film preparations meet organoleptic requirements, uniform weight and thickness, folding power > 300 × and have a pH that meets the pH range that

can be tolerated by buccal, and meets 90 % to 107 % grade requirements. The results of the main evaluation of the swelling index response and residence time response showed values that were not significantly different when compared with the predicted response. This is evidenced by the results of the t test which showed the significance value of the swelling index response of 0.100 and the response significance of the residence time of 0.079. The response of the mucoadhesive strength produced by the optimum formula showed significantly different results compared to the predicted response. This is evidenced by the results of the t test which shows a significance value of 0.017. Significant differences in the mucoadhesive response showed that in this study there were factors other than HPMC and SCMC which were not successfully controlled and influenced the results of the study.

Identification of salbutamol sulphate buccal film spectra (Figure 7) shows that there is a peak at wave number 1 645.85 cm^{-1} which shows C = O; 3 349.12 cm^{-1} which show OH group; 1 042.57 cm^{-1} which shows CO function group; 1 595.88 cm^{-1} which shows the CC group; 1 075.73 cm^{-1} which shows the S = O group, and 838.02 cm^{-1} which shows the C = H group. FTIR testing of pure salbutamol sulphate (Figure 6) and the salbutamol sulphate buccal film showed that the spectra produced were in accordance with the characteristic spectra of pure salbutamol sulphate and there was no fluctuating band shift at the wavelength produced. Interpretation of spectral overlay data (Table 10) shows that the production of salbutamol sulphate buccal film preparations with HPMC and SCMC polymers did not show any interaction that could alter the salbutamol sulphate functional group so that it did not affect the therapeutic effect of salbutamol sulphate.

Based on the results shown in Figure 8 it can be seen that the test results of the percent release of salbutamol sulphate in vitro on the three optimum replication formulas were 88.458 % to 95.705 %. The drug release profile is influenced by the second nature of the polymer used. HPMC K4M has a high viscosity of 4 000 mPa s[8]. Films that only use high concentrations of HPMC can reduce release. The higher the concentration of the polymer, the drug release decreases because it takes time to wipe and dissolve the drug from the polymer matrix[22]. CMC Na has high water solubility and is hygroscopic. Drug release will occur faster if the polymer absorbs water faster and experiences swelling. Films with CMC Na expand and form a layer of gel that opens on the surface of the film. The polymer molecule that is loosely bound to the film is easily eroded, allowing increased drug release[18]. The optimum formula composition consisted of 11.346 mg HPMC and 13.654 mg CMC Na, the dominant component of CMC Na caused the drug release to occur faster.

Conclusion

The combination of HPMC and SCMC could give the optimum response in the buccal film preparations.

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