

Optimization of Mucoadhesive Buccal Film Dosage Form of Sodium Valproate using a Simplex Lattice Design Approach

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ABSTRACT

The primary choice as an anticonvulsant for partial epilepsy, bipolar disorders (psychotic illnesses), and migraine medication is sodium valproate. Many dosage forms designed for the modified release of sodium valproic in tablets have disadvantages, including frequent use and increased toxicity. Therefore, it is necessary to design other dosage forms for the patient and maintain the therapeutic dose. The mucoadhesive buccal film was selected to overcome these problems. In the preparation of these films, this study used variations of chitosan and sodium carboxymethylcellulose (SCMC) as a carrier by solvent casting technique using the simplex lattice design approach. Several parameters characteristic, such as weight, film thickness, surface pH, swelling index, measurement of fold resistance, mucoadhesive residence time, uniformity of drug content and percentage of drug release, were selected as dependent variables. These results showed that the selected polymers influence the thickness, swelling index, and mucoadhesive residence time. The simplex lattice design analysis by the software design expert 10.0 showed the recommendation of optimum parameters desirability ratio of 0.64:0.36 for chitosan and SCMC in a film. The dissolution test was performed to determine the recommended release profile of mucoadhesive buccal film. According to Michaelis-Menten kinetics, the Kinet DS 3.0 software obtained a fitting model for the release profile.

Keywords: Mucoadhesive Buccal Film, SCMC, Simplex lattice design, Sodium valproate.

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INTRODUCTION

Buccal drug delivery systems have advantages such as excellent accessibility, presence of smooth muscle and relatively immobile mucosa. Therefore, it is suitable for administration of retentive dosage forms, direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first-pass metabolism leading to high bioavailability, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritates the mucosa, painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release systems for local or systemic actions.^{1,2}

The ideal candidates in the buccal delivery system include drugs that are easily absorbed only by passive diffusion, are odorless and have a molecular weight between 200–500 daltons, have natural lipophilic and hydrophilic properties,

are tasteless and have a stable pH, which is very good for delivery systems. Banarjee *et al.* (2015) reviewed drugs with high potential in developing fast dissolving film preparations.

Valproic acid and its pharmaceutically acceptable salts are useful for treating various forms of epilepsy and certain other disorders. This acid is considered first-line therapy for treating petit mal, monoclonic seizures, generalized and partial motor seizures, absence and infantile spasms. It was also recently approved for treating partial epilepsy, bipolar disorders (psychotic disorders) and migraine.

Pharmacokinetically, it can bind very high protein at 87–95% and low clearance at 6–20 mL/h/kg (Leppik and Birnbaum, 2010). It is classified as a class 2 Biopharmaceutics Classification System (BCS) drug, with low solubility and high permeability. Various attempts have been made to overcome the solubility problem by converting it to Salt, solid and hygroscopic. This hygroscopicity is a problem in the production of compressed tablet formulations.

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Sodium valproate has been developed in oral, intra parenteral, and rectal dosage forms⁶ and transdermal patches.⁷ Even for repeated use, delayed-release tablets have also been developed. Drugs with doses not exceeding 125–325 mg are more suitable in the form of extended-release products. They can provide several advantages, including limiting the size of the delivery system dosage, reducing the frequency of dosing twice daily, avoiding first-pass metabolism, increasing patient compliance and maintaining therapeutic effect with a single daily dose.³⁻⁷

The buccal delivery route may be useful in treating chronic diseases such as epilepsy. The absorption can be promptly terminated in case of toxicity by removing the dosage. It is also possible to administer drugs to patients who cannot be dosed orally. However, buccal preparations should be made in a thin, small film size for easy application. The preparation is formulated as a matrix with mucoadhesive ability to maintain long contact with the buccal area and release the active ingredients. This matrix acts by swelling or dissolving, undergoing surface erosion. Subsequently, the surface area of the matrix decreases with time and concomitant drug release. The release mechanism across the membrane involves diffusion of water through a membrane into the interior of the nucleus, dissolution and then diffusion of the drug into the surrounding fluid.⁸

The pharmaceutical oral adhesive delivery system should ideally contain mucosal adhesives, penetration promoters, and enzyme inhibitors. Mucosal adhesives are used to maintain close and long-term contact between the formulation and the absorption site. Meanwhile, permeation enhancers are mediated by the mucosa (transmucosal delivery) or drug penetration into the deepest layers of the epithelium (mucosal delivery). Enzyme inhibitors protect the drug from degradation by mucosal enzymes. The barrier properties of the buccal mucosa are a major limitation in developing oral adhesive delivery systems. In manufacturing mucoadhesive buccal film, it is necessary to pay attention to critical factors, such as the choice of polymer. This preparation uses a combination of chitosan polymer and sodium carboxymethylcellulose. Chitosan was selected because it can swell with very slow erosion ability as a film. One of the limitations is that its mucoadhesive properties are reduced when applied to a neutral pH of more than 6.5. This is due to the reduced ionic interaction between the chitosan's positively charged amino groups and the mucosal layer's negative charge. To overcome the chitosan polymer shortage, adding another polymer, such as SCMC to the preparation is necessary. SCMC can protect the adhesion of the product to body tissues from damage. It is also used to localize and modify the release kinetics of the active ingredient. SCMC has a COO- group in an acidic environment, therefore, the bond that will occur with mucosal components is hydrogen bonding. Based on the study of Irawan and Farhana (2011) using a combination of chitosan and SCMC for manufacturing the theophylline tablet mucoadhesive system, the optimum

formula was obtained, resulting in theophylline release kinetics at chitosan 8.38–10.91% and SCMC 28.84–29.09%.

MATERIAL AND METHODS

Material

The tools used were Double Beam UV/Vis Spectrophotometer (Simadzu 1280), Analytical Scale (OHAUS Pioneer) with a sensitivity of 0.0001 g, Micro Pipette (SOCOREX) 50–1000 L, centrifuge (Effendorf Minispin), glass tools such as measuring flasks, beakers, measuring cups, test tubes and other laboratory support equipment.

The materials used are Sodium valproate obtained from PT. Otto Pharmaceutical Lab, Depacote ® Extended Release (AbbVie Ltd, Imported and packed by PT. Abbott Indonesia), Chitosan from Sigma Aldrich, Carboxymethyl cellulose-Na (Bratachem), Propylene glycol (Bratachem), Pharmacoat 606 (Bratachem), Acetic acid (Bratachem).

Optimization of Mucoadhesive Buccal Film Sodium Valproate

The optimization was performed on the Chitosan and SCMC bases by using the SLD design, and the concentrations were selected as independent variables in 8 runs.

Manufacture of Mucoadhesive Buccal Film

Mucoadhesive buccal film sodium valproic of Chitosan/SCMC and their combinations were prepared by the solvent-casting method. Furthermore, SCMC was left overnight in water solvent at room temperature to produce a clear, bubble-free solution. Chitosan was dissolved using 1% acetic acid and stirred with a magnetic stirrer at 500 rpm for 2 hours until all the mass was dissolved. Sodium valproate powder was dissolved in propylene glycol and citric acid, and the mixture was homogenized with a varimixer. The solution is poured into molds and allowed to dry at room temperature, forming a flexible film. Pharmacoat 606 was dissolved in 95% ethanol and poured into a mold as a backing membrane.

Formulation of Mucoadhesive Buccal Film Sodium Valproate

The formula design was made using the proportion ratio of chitosan and SCMC concentrations using design expert 10.0 with the simplex lattice method, and the composition was obtained (Table 1).

Evaluation of Mucoadhesive Buccal Film Sodium Valproate (Table 2)

Weight

The weight and content uniformity method determined the uniformity test of the preparation. Weight uniformity is determined based on the number of weight deviations from the average of all tested data. The test was conducted by randomly weighing 20 films from each formula using an analytical balance. The average and standard deviation of each formula

Table 1: Design Optimization Result of Mucoadhesive Buccal Film Sodium Valproate

Material	Formula of mucoadhesive buccal film (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Sodium Valproat	250	250	250	250	250	250	250	250
Chitosan	0	11,25	33,75	45	22,5	0	45	22,5
SCMC	45	33,75	11,25	0	22,5	45	0	22,5
Propilenglikol	60	60	60	60	60	60	60	60
Pharmacoat 606	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Citric Acid	3	3	3	3	3	3	3	3
Total	300	300	300	300	300	300	300	300

Note F1-F8 = Formula 1 – Formula 8

were then calculated.

$$CV = \frac{SD}{X} \times 100\%$$

Thickness of Film

The uniformity of the film size affects the ease of use of the film, ranging from 0.5–1 mm with a diameter from 1–2 cm.

Surface pH

The pH test of the film surface was conducted to determine the pH of the resulting film. The resulting film should have a neutral pH to prevent irritation of the human mucosa. The surface pH test was carried out by first soaking the patch in a phosphate buffer solution of pH 6.8 for 2 hours at room temperature. The pH measurement was performed by dipping the digital meter into the solution medium before recording.

Swelling Index

Patches were cut into $1 \times 1 \text{ cm}^2$ percentage moisture absorption, weighed accurately, and immersed in 50 mL phosphate buffer pH 6.8. They were removed and weighed at 10, 20, 30 minutes intervals until a constant weight was obtained.

Measurement of Folding Endurance

Three patches of each formulation of size $2 \times 2 \text{ cm}^2$ were cut using a sharp blade, and the endurance was determined by repeatedly folding a small strip of the patch at the same place until it broke. The time the patch could be folded at the same place without breaking gave the value of folding endurance, and the mean value was then calculated.⁹

Mucoadhesive Residence Time

The Mucoadhesion time test measures how long the resulting film can stick to the rabbit mucosa.¹ The film was moistened with phosphate buffer pH 6.8 and attached to the Buccal mucosa to the watch glass by applying pressure for 20 seconds. The watch glass was hung and immersed in 200 mL of phosphate buffer pH 6.8 (temperature $37 \pm 0.5^\circ\text{C}$) with a stirring speed of 50 rpm to stimulate the buccal cavity environment.¹⁰

Drug Content Uniformity

The content uniformity test randomly took about 10 films and then cut them into small pieces. Each film was dissolved in 100 mL phosphate buffer pH 6.8 and sonicated for 15 minutes. Subsequently, 1-mL of the solution was taken from 100 mL of phosphate buffer pH 6.8, transferred to a 10 mL volumetric

flask and added 2 mL of methanol and 0.8 mL of iodine solution. The solution was allowed to stand for 30 minutes, and then chloroform was added until the volume was reached. The absorbance was measured using a Double Beam Ultraviolet-visible Spectroscopy (Shimadzu 1280) at a wavelength of 361 nm, and the obtained values were recorded.

Preparation of Standard Stock of Sodium Valproate and Reagent Solution

Stock standard solutions of sodium valproate 800, 200 and 50 g/mL, prepared separately in methanol, were reacted with Iodine. Sodium valproate (5 mM \approx 1.2 mg/mL) in chloroform and iodine (5 mg/mL).

Calibration Graph

Aliquots (200–1600 L) of standard stock solution of sodium valproate (50 g/mL) were transferred into 10 mL volumetric tubes. The volume was adjusted to 2 mL with methanol and 0.8 mL, and iodine solution was added. The solution was allowed to stand for 30 minutes, then refined with chloroform. The absorbance was measured at 361 nm concerning the standard solvent, and the obtained values were plotted against concentrations to create a calibration graph.

Measurement of Dissolving Time

Type II dissolution test was used for in vitro test of the buccal film release. The dissolution media used phosphate buffer (pH 6.8) 900 mL, temperature $37 \pm 0.5^\circ\text{C}$ and speed of 50 rpm. The film is attached to the padel through a waterproofing adhesive. Furthermore, 5 mL samples were taken at intervals of 5, 10, 15, 30, 45, and 60 minutes, and the same amount of dissolution medium was added with phosphate buffer to maintain equilibrium conditions. The 5 mL sample was transferred to a 10 mL volumetric flask with an additional 2 mL of methanol and 0.8 mL of Iodine. The solution was allowed to stand for 30 minutes, and then chloroform was added until the volume was reached. The absorbance was measured with a Double Beam UV-Vis Spectrophotometer (Simadzu 1280) at a wavelength of 361 nm, before recording the values.¹¹

RESULT AND DISCUSSION

Unsystematic description of the initial matrix without the active compound followed by important qualities related to the release of the active drug while discussing the meanings and correlations of the data.

In this study, computer software was used to understand the relationship between polymers (chitosan and SCMC) widely used as mucosal adhesive polymers. The results show that computer software and the design of experiments can reduce the number of experimental formulations and predict the optimal buccal sodium valproate formulation with a mucosal adhesive film with appropriate properties (Table 3 and 4).

Figure 1 shows the thickness of film test results, where weight and swelling index decreased linearly with the effect of reducing SCMC concentration. The results show that the swelling index value with SCMC concentration produces a larger value due to the stronger water absorption ability.

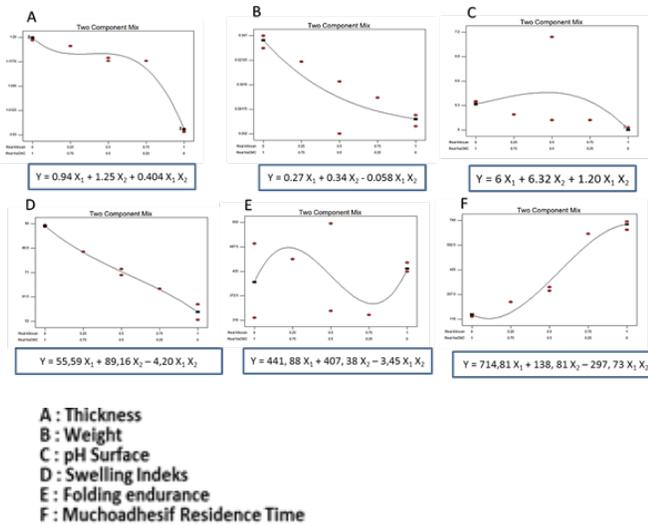


Figure 1: The contour plot of predicted pre-model formulations : (A) thickness, (B) weight, (C) pH Surface, (D) swelling index, (E) folding endurance and (F) mucoadhesive residence time.

Hydrophilic polymers will increase the ability of the wetted film and make it easier for water to penetrate the film. The swelling index value decreased with increasing the concentration of chitosan.

The surface pH measurement results of the effect of chitosan and SMSC showed that it had met the buccal pH range of 5.6–7, thereby corresponding to prevent possible irritation. The folding resistance results also confirmed that the value of all formulations is more than 300 times. It can be seen that the resulting film meets the requirements, namely the preparation is stated to be good with a folding resistance value greater than 300 times.

The mucoadhesive value was influenced by the polymer’s solubility, the coefficient of hydrogen bonding capacity, the swelling index, the concentration of the polymer and the environment (Figure 2). The results showed that increasing the concentration of SCMC chitosan and decreasing chitosan will increase the mucoadhesive power. This factor is influenced by the solubility of the polymer, which affects corrosion when interacting with the environment. Oral membranes with low



Figure 2: Mucoadhesive buccal film sodium valproate

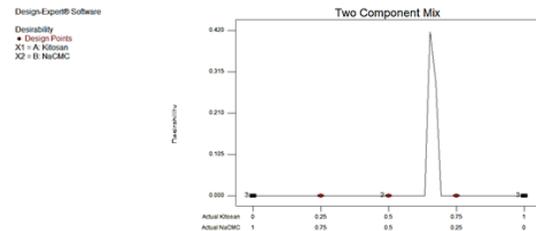


Figure 3: Desirability value chart

polymer concentrations reduce the number of chains per unit that will penetrate and cause an imbalance of interactions. Increasing the amount of polymer in the mucosa can prolong the duration and increase the resistance to mucosal adhesion.

The analysis using software design expert 10.0 shows that chitosan and SCMC polymers can increase mucoadhesive abilities, which will support the preparation to last longer in the environment and release drugs optimally. The optimum formula was determined based on the highest predictive mucoadhesive strength. Based on Figure 3, the optimum formula was selected with a concentration ratio of Chitosan: SCMC = 0.64:0.36.

The results of the experimental preparations carried out by t-test analysis showed no significant difference between the predicted response and the optimization formula with a Sig (2-tailed) Equal variances assumed value of 0.992.

Table 2: Results of mucoadhesive buccal film test for sodium valproate

Response	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
Thickness (mm)	0,25 ± 0,01	0,23 ± 0,01	0,17 ± 0,01	0,16 ± 0,01	0,18 ± 0,01	0,26 ± 0,01	0,15 ± 0,01	0,19 ± 0,01
Weight (gm)	0,331 ± 0,16	0,32 ± 0,36	0,291 ± 0,59	0,268 ± 0,81	0,262 ± 1,03	0,341 ± 1,23	0,277 ± 1,46	0,304 ± 1,68
Content uniformity	248,62	244, 51	233,05	244,7	225,12	247,95	229,61	233,24
Surface pH	6,35 ± 0,13	6,19 ± 0,09	6,12 ± 0,09	6,03 ± 0,08	7,14 ± 0,10	6,34 ± 0,08	6,03 ± 0,08	6,12 ± 0,09
Swelling indeks	89,43 ± 2.39	79,10 ± 2.10	64,6 ± 2.42	58,56 ± 4.5	69,96 ± 3.21	88,8 ± 2.35	52,56 ± 1.72	72,3 ± 2.3
10	43	55	25	17	28	53	22	29
20	87	64	30	43	47	79	42	45
30	98	84	54	65	62	81	58	63
Folding endurance	506	466	324	457	557	316	434	334
Mucoadhesive residence time (minute)	126	220	655	680	315	135	733	290

Table 3: Analysis ANOVA

No	Parameter	Mean ± SD	CV	P	Remark
1.	Thickness	0,15 ± 0,024	2,08	0,0007	Significant
2.	Weight	0,30 ± 0,018	6,12	0,0831	Not significant
3.	Surface pH	6,29 ± 0,41	6,59	0,7164	Not significant
4.	Swelling Indeks	71,92 ± 2,30	3,20	0,0005	Significant
5.	Folding Endurance	424 ± 107,07	25,24	0,8068	Not significant
6.	Mucoadhesive Residence time	394,25 ± 62,96	15,97	0,0023	Significant

Table 4: Data confirming the optimization formula for predictions with a ratio of chitosan : SCMC = 0.64:0.36

Response	Prediction	Optimasi
Thickness	0.18	0.14
Weight	0.29	0.27
Surface pH	6.24	6.20
Swelling Index	67.26	65.35
Folding Endurance	424	388
Mucoadhesive Residence time	480	510

Table 5: Model Fitting for optimization formulation

Order of reaction (zero)	Order of reaction (first)	Korsmeyer-peppas	Mathematical model				
			Weibull	Hickson-crowell	Higuchi	Michaelis-menten	Hill equation
0.0934	0.1326	0.4499	0.3739	0.1188	-0.4441	0.8114	0.2935

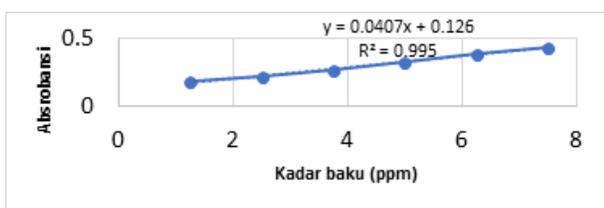


Figure 4: Standard curve of sodium valproate

Solubility Measurement

Solubility is the process of dissolving a drug from preparation in a certain medium to determine the release profile of mucoadhesive buccal film of sodium valproate. The test was carried out at 370°C, and the dissolution medium was phosphate buffer pH 6.8. In the determination of the standard curve for sodium valproate in isotonic phosphate buffer, the absorption was measured using a Simadzu 1280 Double Beam UV/Vis Spectrophotometer at a maximum wavelength of 361 nm. The standard curve was obtained from the relationship between concentration and absorption (Figure 4). The experimental results in Figure 2 show the standard curve for sodium valproate following the linear regression line equation $Y = 0.0407x + 0.126$ with an r-value of 0.995. This data was used to determine the concentration of sodium valproate.

The results of the drug release test using the Kinet DS3.0 software obtained a fitting model for the optimum mucoadhesive buccal film formula (Table 5). This model can be influenced because the polymer used have an impact on hydrogen bonding factors, solubility and polymer erosion ability when interacting with environmental media.

The optimization formula follows Michaelis-Menten kinetics, and cross-linking occurs between chitosan and SCMC. This binding mechanism is due to the nature of SCMC as it dissolves in water with chitosan to form hydrogels, closing matrix cavities and preventing drug release. Changes in water-insoluble properties release the drug onto the film in a stable system. The hydrophilic polymer can expand into hydrogels in

a liquid medium due to the cross-linked matrix, which makes them insoluble and absorbs only water.

CONCLUSION

Mucoadhesive film of sodium valproate appears to be an acceptable dosage form for treating epilepsy. This film showed acceptable and desirable properties, and the application of the design is a useful tool in developing the desired dosage form.

All formulas meet the requirements of the Indonesian Pharmacopoeia based on the physical assessment supported by the results of the factorial planning analysis. The polymer and the concentration used can affect the release profile of the drug in vitro. The optimal formula for mucoadhesive buccal film was the concentration ratio of Chitosan:SCMC = 0.64:0.36.

PATENTS

There is no patent resulting from the work reported in this manuscript.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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