Indonesian Journal of Pharmacy

VOL 32 (1) 2021: 43–51 | RESEARCH ARTICLE

Optimization of Hydroxy Propyl Methyl Cellulose and Carbomer in Diltiazem Hydrochloride Mucoadhesive Buccal Film

Lina Winarti, Bagus Tri Laksono, Lusia Oktora Ruma Kumala Sari

Department of Pharmaceutics, Faculty of Pharmacy, University of Jember East Java Indonesia

Info Article

Submitted: 07-12-2020
Revised: 03-02-2021
Accepted: 13-02-2021

*Corresponding author
Lina Winarti

Email:
lina.winarti@unej.ac.id

ABSTRACT

Diltiazem hydrochloride (HCl) is a drug with low bioavailability due to the high rate of the first-pass metabolism and a short half-life of the drug (3-5h); hence, mucoadhesive buccal films were made to overcome this weakness. The bioavailability of Diltiazem HCl may increase if the buccal preparations can make good contact with the mucosa for a sufficient amount of time. Therefore, in this study, two polymers, Hydroxy Propyl Methyl Cellulose (HPMC) and Carbomer were combined to obtain good film characteristics, especially in residence time and mucoadhesive strength. This study aimed to optimize the amount of HPMC and Carbomer needed and evaluate the release kinetics of Diltiazem HCl from the mucoadhesive buccal film. The formula was prepared by the solvent casting method and optimized with the design expert software, while the release kinetics and mechanism were evaluated using the DDSolver program. The optimum amount of polymer obtained from optimization was 40mg of HPMC and 10mg of Carbomer. The FTIR spectra showed there was no interaction between Diltiazem HCl and other excipients. The dissolution model of Diltiazem HCl from buccal mucoadhesive film follows Korsmeyer-Peppas. The release exponent (n) of 0.55 shows a non-fickian/anomalous diffusion release mechanism. These mechanisms represent drug release controlled by a combination of diffusion and erosion. This study concluded that the buccal film was successfully formulated by using a combination of HPMC and Carbomer with the potential to increase Diltiazem HCl bioavailability and half-life by increasing its contact time and controlling the release.

Keywords: Diltiazem HCl, HPMC, Carbomer, Mucoadhesive Buccal Film

INTRODUCTION

Hypertension is one of the cardiovascular diseases that have a high prevalence in several countries in the world (WHO, 2012). Diltiazem HCl is usually used as antihypertensive, antiarrhythmic, and anti-angina. Diltiazem HCl affects smooth muscle relaxation from the blood vessels, causing peripheral vascular resistance (Patel *et al*., 2015).

Diltiazem HCl has a half-life of 3-5h in the body (Sweetman, 2009). If given orally, Diltiazem HCl will experience the first-pass metabolism; therefore, its bioavailability is low (40%) (Wang *et al*., 2016). In order to avoid the first-pass metabolism, Diltiazem hydrochloride has been formulated into a mucoadhesive buccal film. The buccal film has the advantage of bypass first-pass metabolism; hence, the bioavailability of drugs through this route will be better when compared with a conventional oral formulation.

Buccal films are flexible, elastic, and soft but are still able to stay in the mouth. So the system can prolong the duration of the medicine residence time in the buccal absorption site, reduce the frequency of use (Hagerstrom, 2003), and modulate the permeability to epithelial tissue by loosening the intercellular junction (Lehr, 1999). The length of residence time depends on the bioadhesive strength of the polymer used (Peh and Wong, 1999). The polymers used for mucoadhesive buccal film preparations in this study were Carbomer and HPMC.

Carbomer is an anionic polymer that can bind to the mucosa through hydrophobic interactions, hydrogen bonds, and Van der Walls bonds. It is a polyacrylic acid class polymer which is insoluble in water and will expand to form a gel when hydrated (Woodley, 2001). Carbomer has a flexible chain and has non-abrasive characteristics

when it is hydrated, thereby reducing the risk of tissue damage when it comes into contact with friction (Carvalho *et al*., 2010).

HPMC is combined with carbomer because it is a hydrophilic nonionic polymer with mucoadhesive strength lower than anionic polymers (Mortazavi and Moghimi, 2003) but capable to form a flexible film, biocompatible, and biodegradable (Byun *et al*., 2012). HPMC is also a bioadhesive with excellent water absorption capacity and is not easily eroded by saliva (Garg and Kumar, 2007). According to Roda *et al*. (2018), the use of a combination of HPMC and carbomer was the best carrier in buccal patches for the delivery of Hydrochlorotiazid and Atenolol compared with the use of a combination of Sodium Alginate - HPMC, Carbomer – Carboxymethylcellulose (CMC Na), or HPMC - CMC Na.

Based on the previous description, it is essential to determine the effect of HPMC and Carbomer combination on Diltiazem HCl buccal film swelling index, mucoadhesive strength, and residence time. FTIR analysis and drug release study were also conducted to evaluate the release kinetics and mechanism.

MATERIAL AND METHODS

Diltiazem HCl was a gift sample from Kimia Farma company (Indonesia), HPMC K4M, Carbomer, Glycerin, Ethanol 96%, KH_2PO_4, NaOH, HCl were purchased from PT. BrataChem (Indonesia), and buccal mucosa of male goats aged 3-4 years obtained from a nearby slaughterhouse.

Table I. The composition of the buccal film Diltiazem HCl formula

Materials	F1	FA	FB	FAB
Diltiazem HCl	0.64g	0.64g	0.64g	0.64g
HPMC	0.32g	0.64g	0.32g	0.64g
Carbomer	0.16g	0.16g	0.32g	0.32 g
Glycerin	0.3mL	0.3mL	0.3mL	0.3mL
NaOH	1.6mL	1.6mL	1.6mL	1.6mL
Ethanol 95%	5mL	5mL	5mL	5mL
Distilled water	40mL	40mL	40mL	40mL

Preparation of Mucoadhesive Buccal Film of Diltiazem HCl

The buccal film was prepared by the solvent casting method. Carbomer and HPMC polymers were weighed and then dispersed in distilled water until a clear gel formed. The mixture of the polymer was mixed until homogeneous and added with glycerin. Diltiazem HCl was dissolved in a mixture of water:ethanol of 1:5 and NaOH 1N. Diltiazem HCl solution was then added to a mixture of polymer and glycerin and stirred using a magnetic stirrer for 20min at a speed of 100rpm. The film mixture was poured into the mold and left overnight to remove air bubbles. The film in the mold was dried using an oven at 45°C for 24h. The dry film is cut into a size of 2x2 cm ($4cm^2$). The composition of the formula for 16 films (Table I).

Mucoadhesive buccal films evaluation

Organoleptic property

The buccal film's organoleptic properties observed include color, odor, taste, texture, and surface conditions.

Weight uniformity

Three films of each formula were weighed using digital scales (Semalty *et al*., 2008) the mean and standard deviation of the measurements were calculated.

Thickness

The thicknesses of the three films were measured using a micrometer screw gauge at five different points: in the middle and the four corners of the film (Semalty *et al*., 2008). The average and standard deviation (Table II).

Folding endurance

Folding endurance was examined by repeatedly folding at the same place for up to 300 folds (Alagusundaram *et al*., 2009).

Surface pH

For determination of surface pH, three films of each formulation were allowed to swell in 5mL of distilled water for 2h on the agar plate/petri-dish. The surface pH was measured by using a pH meter placed on the surface of the swollen buccal film. The mean value of three readings was recorded (Salehi and Boddohi, 2017).

% Drug Content

The drug content determination was done by dissolving 2x2cm film in 100mL phosphate buffer (pH 6.6), and the absorbance was observed at a wavelength of 237nm. The film's Diltiazem content was calculated using a calibration curve prepared from the Diltiazem HCl working standards at 4.1, 6.0, 8.3, 10.3, and 12.0ppm obtained from diluting a 100ppm Diltiazem HCl stock solution.

The percentage of drug content was calculated with equation 1, and the average of % Diltiazem HCl content from three films was recorded.

$$\% \ Content = \frac{Experiment\ Resul\ content}{Theoretical\ content} \ x100\% \quad \text{.....(1)}$$

Swelling Index

One film was weighed (W0) and placed on a petri dish containing 5mL phosphate buffer. The film was allowed to expand. The film was then weighed (Wt) at intervals of 5, 15, 30, and 60min (Puratchikody *et al*., 2011). The swelling index was calculated using the following equation (2):

$$\% \ Swelling\ Index = \frac{Wt - W0}{W0} \quad \text{.....(2)}$$

Mucoadhesive strength

Mucoadhesive strength was evaluated using the Texture Analyzer by attaching the film to the probe's tip. The probe gives a force of 500 gF with a speed of 0.5mm/s for 60 s (Skulason *et al*., 2009). The probe is then lifted at a rate of 1mm/s. The force required until the film detaches from the buccal tissue was recorded in grams force (gF).

Mucoadhesive Residence Time

The film was attached to the buccal goat tissue and onto a glass object placed on the edge of a 1000 mL glass beaker. One side of the film was moistened with phosphate buffer medium pH 6.6. The beaker glass was filled with 500mL phosphate buffer medium of pH 6.6 at 37°±0.5°C. The medium was stirred at 50 rpm and observed for 8h (Patel *et al*., 2007; Roda *et al*., 2018).

Formula Optimization

The swelling index, mucoadhesive strength, and residence time of Diltiazem HCl mucoadhesive buccal film were analyzed using design expert software version 11. The optimum formula was obtained from the overlay of the three responses.

Optimum Formula Verification

Predicted responses from the factorial design to the observation results were compared statistically with the One-Sample T-test using a confidence level of 95%. The p-value >0.05 shows no difference between the predicted responses and the observed responses (Arwani, 2017).

Fourier Transform Infrared (FTIR) Analysis

FTIR analysis aimed to determine whether there was an interaction shown by HPMC and Carbomer with Diltiazem HCl. Scanning was done at 4000-600cm^{-1}. Each spectrum was compared and observed for the presence or absence of interactions, as indicated by a fluctuating shift in the absorption band in the optimum formula (El-Maghraby and Abdelzaher, 2015).

Diltiazem HCl Release Study

The drug release was evaluated using paddle-type equipment. The study was done using 500mL of phosphate buffer (pH 6.6) as a dissolution medium, temperature of 37±0.5°C, and stirring speed of 50 rpm. Films containing 40 mg of Diltiazem HCl were attached to the object-glass using cyanoacrylate adhesive. Samples of 5 ml were taken at certain time intervals (0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480min) followed by replacement of the dissolution medium by 5mL. The sample was filtered and analyzed with a UV spectrophotometer at a wavelength of 237 nm (El-Maghraby and Abdelzaher, 2015).

RESULT AND DISCUSSION

The Physicochemical Characteristics

The composition of the Diltiazem HCl mucoadhesive buccal film (Table I). The prepared films were subjected to different physicochemical tests such as weight variation, thickness, content uniformity, swelling index, surface pH, *in-vitro* residence time, and *in vitro* drug release studies. The four-film formulas were transparent, odorless, slightly sweet, supple, dry, and had a smooth surface (Figure 1).

The film formulas have uniform weights and thicknesses indicated by the p-value > 0.05 (Table II). Film weight and thickness are influenced by the amount of polymer used. The more polymer used, the higher the film's weight and thickness, and vice versa.

Based on the folding endurance evaluation, all the films had good flexibility indicated by the film's ability to fold up to >300 folds (Alagusundaram *et al*., 2009). The values revealed excellent film properties.

The pH of the film should meet the ideal pH for buccal application because the acidic or alkaline pH may irritate the buccal mucosa. The film's surface pH meets the pH range that the buccal cavity can accept (5.5-7) (Patel *et al*., 2011); hence no mucosal.

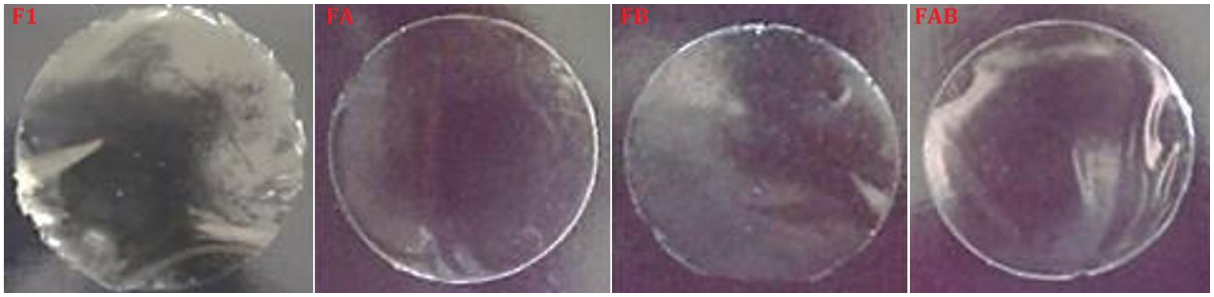

Figure 1. Diltiazem HCl mucoadhesive Buccal Film

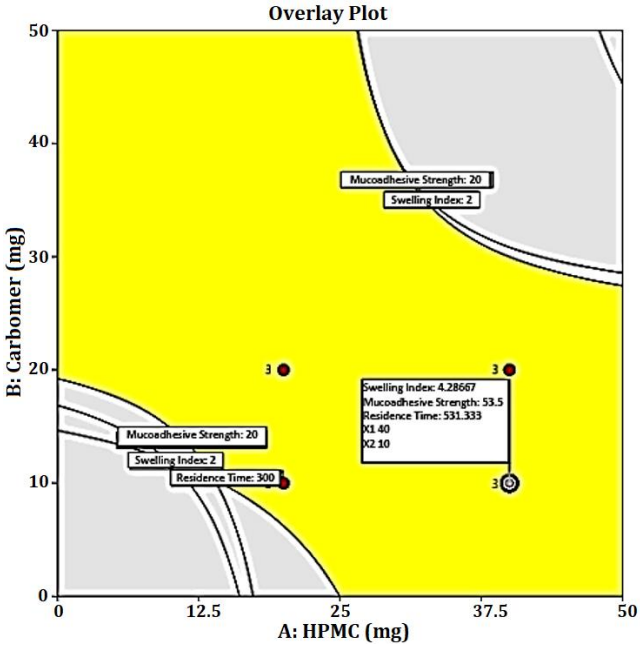

Figure 3. Overlay Plot of Three Responses (shown in Yellow)

Table II. Physical evaluation of Diltiazem HCl mucoadhesive buccal films

	Film weight (mg)	Film thickness (cm)	Folding endurance	Surface pH	% Drug Content
F1	91.7±0.60	0.021±0.001	>300	5.91±0.061	99.16±0.47
FA	95.8±0.25	0.027±0.001	>300	6.00±0.031	97.78±1.08
FB	94.3±0.55	0.025±0.000	>300	5.75±0.059	95.55±1.04
FAB	107.1±1.14	0.029±0.001	>300	5.71±0.051	94.99±1.16

The Calibration Curve

The method for determining Diltiazem HCl is deemed valid when the accuracy, precision, linearity, and detection and quantification limits are within the acceptable values. A serial concentration of Diltiazem HCl (4.1–12.0µg/mL) was observed by UV spectroscopy at the λ_{max} of 237 nm. The calibration curve was the result of observed absorbance values plotted to different concentrations resulted from the serial dilution. The linear regression equation was found to be Y = 0.0577x – 0.0246, R^2 = 0.9995 which depicts the linearity (Figure 2).

The content of diltiazem HCl in the film preparations ranged from 94,99 - 99,16%; therefore, the four formulas had fulfilled the range of required levels in the film preparations, which are 85-115% (Dixit dan Puthli, 2009). The drug content in each film will contribute to its therapeutic effect.

Table III. The results of three buccal film response for optimization

	Swelling index	Mucoadhesive strength (gF)	Mucoadhesive residence time (min)
F1	2.67±0.06	27.93±1.90	350.0±3.61
FA	4.29±0.17	53.63±2.11	531.3± 3.51
FB	2.79±0.05	29.47±0.81	482.1± 3.51
FAB	3.15±0.11	37.43±2.28	514.7± 4.51

Swelling index

Swelling index measurement aims to determine the level of hydration that occurs. The results of the sequential swelling index are as follows FA>FAB>FB>F1 (Table III). The use of a high amount of HPMC and a low amount of carbomers (FA) gives good film hydration, providing the best swelling index. Carbomers have excellent hydration properties than HPMC, but when used at a large amount, the film will be hydrated excessively (overhydration), which results in the removal of the polymer chain in the film. It results in eroded and dissolved films, which reduce the swelling index (Morales and McConville, 2011).

Mucoadhesive strength and residence time

Mucoadhesive strength and residence time evaluation aims to determine the film's attachment strength to the buccal mucosa; thus, the film does not detach although it is exposed to mechanical forces in the oral cavity (Kumria *et al*., 2014). The mucoadhesive strength and residence time results (Table III) as follows: FA>FAB>FB>F1.

Carbomers belong to an anionic polymer group, thus, they have higher mucoadhesive and swelling index strength than HPMC (Morales and McConville, 2011); a better swelling index indicates excellent hydration. On the contrary, carbomers at high concentrations will produce massive hydration; there will be overhydration and reduced adhesive strength due to the polymer chain's decomposition (Peh and Fun Wong, 1999). Thus, a formula with a high amount of HPMC (FA) provides greater mucoadhesive strength than that with a high amount of carbomers (FB). The mucoadhesive residence time is related to mucoadhesive strength. When the mucoadhesive strength increases, the film will need a longer time to detach from the buccal mucus membrane, and vice versa (Roda *et al*., 2018). The results show that all the buccal film formulas exhibited good mucoadhesive strength and residence time.

The formula optimization and verification

The optimum formula was determined from the highest predicting value of three responses with a desirability index close to one. Determination of the optimum area is selected based on the overlay plot generated from three responses. The optimum area is shown in yellow (Figure 3), which shows the amount of HPMC and Carbomer that gives the highest value for the swelling index, mucoadhesive strength, and residence time. Based on the optimization process, six solutions were obtained, then one solution with the highest desirability (HPMC of 40mg and Carbomer of 10mg) was selected as the optimum formula. The optimum formula verification aimed to confirm the factorial design-predicted results with the experimental results. Verification was done using a one-sample t-test with a confidence level of 95%. The predictive response shows no significant difference from the experimental result with a p-value > 0.05.

FTIR analysis

FTIR spectra of the optimum formula, Diltiazem HCl, HPMC, and Carbomer (Figure 4). Diltiazem hydrochloride has O-CH3, amine, acetate, and lactam as functional groups at which the chemical interaction may occur. FT-IR spectral analysis shows no interference to the functional groups as Diltiazem HCl's principle peaks were unaltered in the mucoadhesive buccal film, indicating no interaction between the drug and the excipients.

Release study

The Diltiazem HCl buccal film using a combination of HPMC and carbomer exhibited a controlled release over more than eight hours and can release 95.43% of the drug after 480min. The results are in accordance with Patel *et al*. (2013), who formulated chlorpheniramine maleate tablets using a matrix of HPMC K15M, HPMC K100M, and carbomer, which produced a controlled release over 6h.

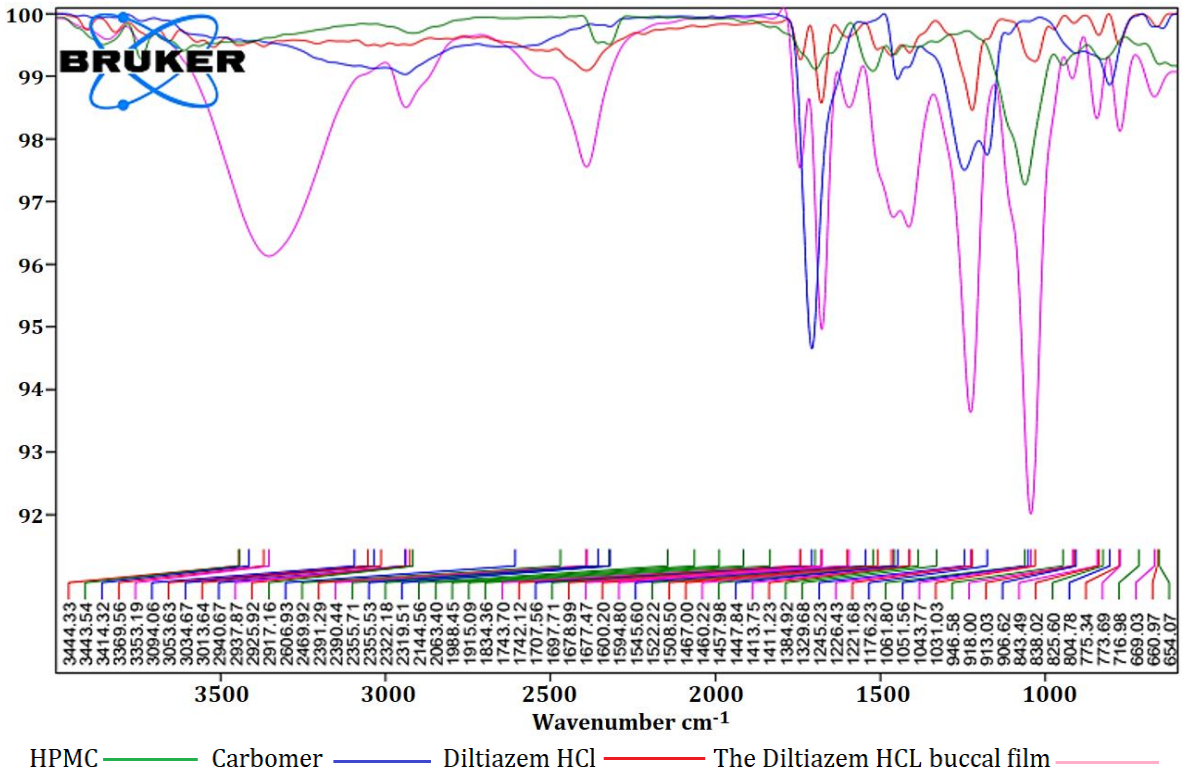

Figure 4.The FTIR result of optimum formula, pure diltiazem HCl, HPMC, and carbomer

Table IV. The dissolution parameters obtained from DDSolver program

Dissolution model	The dissolution model parameters				
	R^2 Adjusted	MSE	WSS	AIC	MSC
Zero-order	0.78	160.74	2250.37	117.76	1.36
First-order	0.95	33.58	470.08	94.19	2.93
Higuchi	0.99	8.24	115.36	73.2	4.33
Korsmeyer-Peppas	0.99	6.18	80.29	69.61	4.57
Hixson-Crowell	0.93	47.13	659.77	99.32	2.59
Hopfenberg	0.95	36.18	470.33	96.2	2.8
Baker-Lonsdale	0.95	34.39	481.51	94.64	2.9
Weibull	0.97	18.35	220.23	86.77	3.43

HPMC K100M produced slower release than the other two polymers, which followed zero-order release kinetics and the Fickian diffusion mechanism.

DDSolver program was used to analyze the release kinetics of Diltiazem HCl from the mucoadhesive buccal film. DDSolver is an add-in program for Microsoft Excel, which is easy to use. The analysis of statistical parameters (table 4) using DDSolver shows that the dissolution model followed the Korsmeyer-Peppas. The Korsmeyer-Peppas is more appropriate for describing the dissolution of Diltiazem HCl from the buccal film because the model has the highest adjusted R^2 and MSC (Model Selection Criterion) but has the smallest MSE (mean square error), WSS (weighted sum of squares), and AIC (Akaike Information Criterion) compared to other models (Nugroho *et al*., 2014). The highest adjusted R^2 and MSC values show the model's best suitability, while the lowest MSE, WSS, and AIC values show high precision of the model (Siswanto *et al*., 2015).

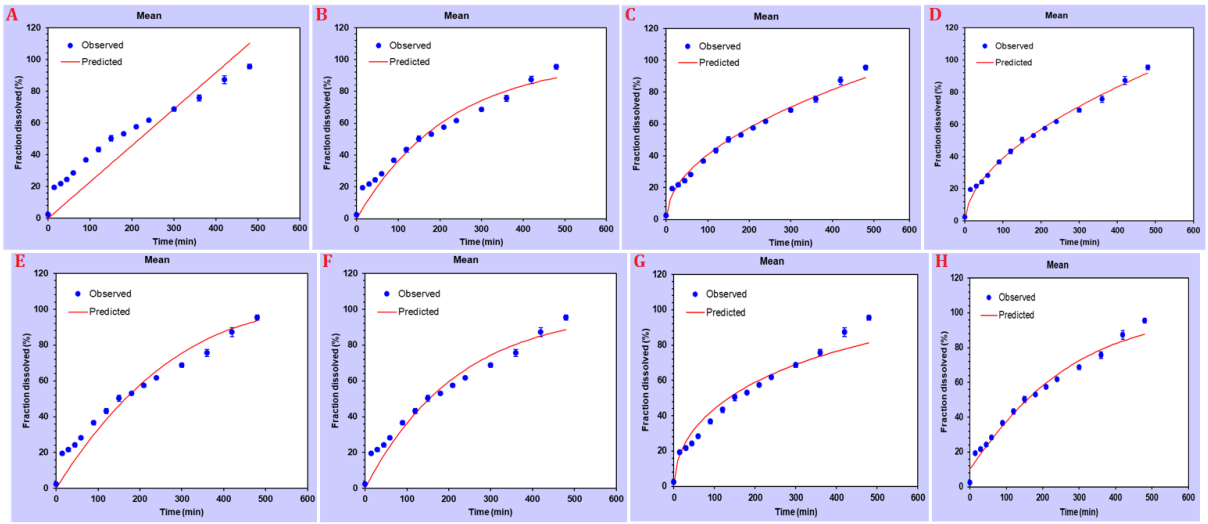

Figure 5: Diltiazem HCl profile of predictive dissolution (Qp) and experimental results (Qo) versus time (n = 6). A Zero order; B First order; C Higuchi; D Korsmeyer Peppas; E Hixson Crowell; F Hopfenberg; G Baker-lonsdale; H Weibull model.

In the Korsmeyer-Peppas equation, the n-value (the release exponent) was 0.55. Based on the n-value, the release of Diltiazem HCl from the buccal film follows the non-fickian/anomalous diffusion release mechanism. This mechanism describes controlled drug release through a combination of diffusion and erosion. Erosion during the release process happens when a large amount of carbomer is used. The film is overhydrated due to the high carbomer content, which removes the polymer chain in the film. Hence, it results in drug release from the eroded matrix. The diffusion happens when carbomer and HPMC are in contact with water. The matrix will not dissolve but will expand in the water to form a gel-layer so that the drug diffuses more slowly (Merchant *et al*., 2006).

The results of curve fitting analysis strengthen the release kinetics determination based on statistical parameters. The curve fitting (figure 5) shows that the Korsmeyer-Peppas model is the most appropriate model to explain the dissolution of Diltiazem HCl from the buccal film using HPMC and carbomer as the polymer. The Korsmeyer-Peppas model provides observation dissolution data (Qo) around the predicted dissolution data curve (Qp). Meanwhile, dissolution modeling with zero-order, first-order, Higuchi, Hixson-Crowell, Hopfenberg, Baker-Londsdale, and Weibull resulted in a more considerable difference between Qo and Qp.

Siswanto *et al*. (2015) also used DDSolver to analyze the release kinetics of Aspirin floating tablet using Methocel K4M CR, NaHCO3, Ethocel, Aerosil, and dicalcium phosphate anhydrous as excipients. Their dissolution data were evaluated using DDSolver conducted by Statistical parameters (R^2 adjusted, AIC, MSC) and Visual goodness of fit (GOF). The results showed the same release kinetics with the Diltiazem HCl buccal film. The Aspirin floating tablets release kinetics followed the Korsmeyer-Peppas model and occurred through anomalous transport, which combines Fickian diffusion and polymer relaxation. Therefore, Methocel K4M CR, NaHCO3, Ethocel, Aerosil, and dicalcium phosphate anhydrous as excipients in the Aspirin floating tablets resulted in the same release mechanism as a combination of HPMC and Carbomer in Diltiazem HCl buccal film.

CONCLUSION

From the study, it can be concluded that the combination of HPMC and carbomer could obtain good film characteristics with a controlled release over 8 hours. The combination also improved residence time and mucoadhesive strength for sufficient contact time to the mucosa. The overall results show the potential combination of HPMC and carbomer to increase bioavailability and half-life of Diltiazem HCl.

ACKNOWLEDGMENT

The authors acknowledge the Faculty of Pharmacy University of Jember for supporting this research.

REFERENCES

Alagusundaram M., Chengaiah B., Ramkanth S., Parameswari SA., Chetty CMS., Dhachinamoorthi D. 2009. Formulation and evaluation of mucoadhesive buccal films of ranitidine. *International Journal of PharmTech Research,* 1(3), 557–563.

Arwani M. 2017. Optimasi kombinasi karbomer 934 dan hpmc terhadap efektivitas gel anti jerawat ekstrak etanolik kulit buah manggis (Garcinia mangostana L.) dengan metode factorial design. Essay. *Universitas Muhammadiyah Surakarta.*

Byun Y., Ward A., Whiteside S. 2012. Formation and characterization of shellac-hydroxypropyl methylcellulose composite films. *Food Hydrocolloids.* 27(2):364–370.

Carvalho FC., Bruschi ML., Evangelista RC., Gremiao MPD. 2010. Mucoadhesive drug delivery systems (review). *Brazilian Journal of Pharmaceutical Sciences*. 46(1):1–17.

Dixit RP., Puthli SP. 2009. Oral strip technology: Overview and future potential. *Journal of Controlled Release,* 139(2), 94–107. https://doi.org/10.1016/j.jconrel.2009.06.014

Donald PL., Gary LM., George KS. 2011. Introduction To Spectroscopy.3rd ed. Bellingham, Washington: Thomson learning.

El-Maghraby GM., Abdelzaher MM. 2015. Formulation and evaluation of simvastatin buccal film. *Journal of Applied Pharmaceutical Science,* 5(4), 070–077. https://doi.org/10.7324/JAPS.2015.50412

Garg S., Kumar G. 2007. Development and evaluation of a buccal bioadhesive system for smoking cessation therapy. *Pharmazie.* 62(4):266– 272.

Hagerstrom, H. 2003. Polymer gels as pharmaceutical dosage forms. Dissertation. Acta Universitatis Upsaliensis Uppsala, Sweden.

Kumria R., Nair AB., Goomber G., Gupta S. 2014. Buccal films of prednisolone with enhanced bioavailability. *Drug Delivery,* 1–8. https://doi.org/10.3109/10717544.2014.920058

Lehr C M. 1999. Lectin-mediated drug delivery: The second generation of bioadhesives. *Journal of Controlled Release*, 65(2000), 19–29. https://doi.org/10.1016/S0168-3659(99)00228-X

Merchant H A., Shoaib H M., Tazeen J., Yousuf RI. 2006. Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxypropyl methylcellulose: A technical note. *AAPS PharmSciTech*, 7(3), 178–183. https://doi.org/10.1208/pt070378

Morales JO., McConville JT. 2011. Manufacture and characterization of mucoadhesive buccal films. *European Journal of Pharmaceutics and Biopharmaceutics,* 77(2), 187–199. https://doi.org/10.1016/j.ejpb.2010.11.023

Mortazavi S., Moghimi H. 2003. Effect of surfactant type and concentration on the duration of mucoadhesion of carbopol 934 and hpmc solid compacts. *Iranian Journal of Pharmaceutical Research*. 2(4):191–199.

Nugroho AK., Binnarjo A., Hakim AR., Ermawati Y. 2014. Compartmental modeling approach of losartan transdermal transport in vitro. Indonesian J. Pharm., Vol. 25 No. 1, 31-38.

Patel BP., Patel DM., Patel JK. 2013. Effect of hpmc/carbopol on the release of chlorpheniramine maleate from matrix tablets. *Indonesian J. Pharm.* Vol. 24 No. 3 : 157 – 162.

Patel AM., Majmudar F., Sharma N., Patel NB. 2015. Assessment of food effect on bioavailability of diltiazem in indian population. *World Journal Of Pharmacy And Pharmaceutical Sciences*, 4(7), 1130–1140.

Patel VF., Liu F., Brown MB. 2011. Advances in oral transmucosal drug delivery. *Journal of Controlled Release,* 153(2), 106–116. https://doi.org/10.1016/j.jconrel.2011.01.027

Patel VM., Prajapati BG., Patel MM. 2007. Design and characterization of chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride. *Acta Pharmaceutica*, 57(1), 61–72. https://doi.org/10.2478/v10007-007-0005-9

Peh KK., Wong FC. 1999. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. *Journal of Pharmaceutical Sciences*, *2*(2), 53–61.

Puratchikody A., Prasanth VV., Mathew ST., Kumar BA. 2011. Development and characterization of mucoadhesive patches of salbutamol sulfate for unidirectional buccal drug delivery. *Acta Pharmaceutica*, 61(2), 157–170. https://doi.org/10.2478/v10007-011-

0011-9

Roda A., Prabhu P., Dubey A. 2018. Design and Evaluation of Buccal Patch Containing Combination of Hydrochlorothiazide and Atenolol. *International Journal of Applied Pharmaceutics*, 10(2), 105–112.

Salehi S., Boddohi S. 2017. New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate*. Progress in Biomaterials,* 6(4), 175–187. https://doi.org/10.1007/s40204-017-0077-7

Semalty M., Semalty A., Kumar G., Juyal V. 2008. Development of mucoadhesive buccal films of glipizide. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1(2), 184–190.

Siswanto A, Fudholi A., Nugroho AK., Martono S. 2015. In vitro release modeling of aspirin floating tablets using DDsolver, *Indonesian J. Pharm*. Vol. 26 No. 2: 94 – 102

Skulason S., Asgeirsdottir MS., Magnusson JP., Kristmundsdottir T. 2009. Evaluation of polymeric films for buccal drug delivery. Pharmazie, 64(3), 197–201. https://doi.org/10.1691/ph.2009.8188

Sweetman S. 2009. Martindale The complete drug reference. 36th ed. *Pharmaceutical Press, London*

Wang YB, Lian ZX., Chen MN., Zhang L., Zhou CY., Wei W. 2016. Bioadhesive drug delivery system of diltiazem hydrochloride for improved bioavailability in cardiac therapy. *Tropical Journal of Pharmaceutical Research*, 15(7), 1375–1380. https://doi.org/10.4314/tjpr.v15i7.4

WHO. 2012. World Health Statistic 2012*. WHO Press, France*

Woodley J. 2001. Bioadhesion: new possibilities for drug administration. *Clinical Pharmacokinetics*. 40(2):77–84.