FORMULATION AND OPTIMIZATION OF CARBOPOL AND ETHYL CELLULOSE AS FLOATING-MUCOADHESIVE SYSTEM OF DILTIAZEM HYDROCHLORIDE TABLET BY FACTORIAL DESIGN

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INTRODUCTION

Hypertension is a degenerative disease that each year has increased the number of patients. Number of patients in Indonesia is estimated at 15 million people. Nearly 50% of patients suffering from hypertension are not aware that tends to be severe hypertension (Syahrini et al., 2012).

Diltiazem Hydrochloride (HCl) is an antihypertensive drug used 3-4 times a day with doses of 30-60 mg (UBM Medica, 2012). Diltiazem HCl has a half life of 3-5 hours (Sweetman, 2009) with the main absorption area in the upper stomach (Kapil et al., 2012) that can be formulated into sustained release dosage gastro retentive system.

The system created is a combination of floating-mucoadhesive. The combination of these systems is expected to overcome the shortcomings of the system when used alone. Floating system floats over the surface of gastric contents when the stomach is full but at the time stomach is emptied and the tablet reaches the pylorus the bouyancy of the dosage may be decreased. If the stomach is full, mucodhesive dosage form not properly adheres may be passage the pylorus due to peristaltic movements of the stomach (Gaykar et al., 2013).

Polymer is one of the essential ingredients to produce a floating-mucoadhesive system that meets the requirements. The polymer used is a combination of Carbopol and ethyl cellulose. The combination of hydrophilic and hydrophobic polymers proved able to control the rate of drug release with high solubility (Nanjwade et al., 2011).

MATHERIAL AND METHOD

Diltiazem HCl (obtained from PT Dexa Medica), Carbopol (BRATACO Chemica), ethyl cellulose (Hercules), HPMC K4M (BRATACO Chemica), sodium bicarbonate, dibasic calcium phosphate (BRATACO Chemica), magnesium stearate (BRATACO Chemica), Potassium Chloride (KCl) (BRATACO Chemica), Hydrochloric Acid (HCl) 32% (BRATACO Chemica), gastric local male rabbits .

Dissolution tester (Logan Instrument), spectrophotometer (Genesys Type 10S UV-Vis), tablet friability tester (Pharmeq type TAB), digital analytical balance (Ohaus Adventure), single punch tablet press, tablet hardness tester (Stokes-Monsanto), flowability tester (Pharmeq), texture analyzer (TaXt plus Stable Micro Systems, UK), and software data processing (Microsoft Office Excel 2007, IBM statistic 21, and Design Expert 8.0.7.1).

Formula of Diltiazem HCl Tablet

The composition of the complete formula can be seen in Table 1.

Table 1 Formula

Formula	Formula (mg)			
	I	II	III	IV
Diltiazem HCl	90	90	90	90
Carbopol	60	150	60	150
Ethyl celulose	30	30	90	90
HPMC K4M	90	90	90	90
$NaHCO_3$	75	75	75	75
Dibasic Ca Phosphat	150	60	90	0
Mg stearat	5	5	5	5
Weight of Tablet (mg)	**500**	**500**	**500**	**500**

Preparation of Diltiazem HCl Tablet

Tablet was made by direct compression method. All the ingredients except magnesium stearate were mixed for 10 minutes and then mixed again with the magnesium stearate for 5 minutes. The powder flow properties and homogeneity of active ingredient were evaluated. The powder mixture was compressed into tablets with a single punch tablet tablet machine. Tablet hardness was controlled between 4-8 kg. Tablets are evaluated hardness, friability, uniformity of dosage, buoyancy, mucoadhesive strength and dissolution testing.

Evaluation of Physical Properties of the Tablet

Evaluation of tablet hardness was done using Pharmeq Stokes-Mosanto Hardness Tester. Friability test was done using 20 tablets and 3 times of replication. Terms of losing weight allowed is ≤1% (USP 30, 2007).

Tablet Content Uniformity Evaluation

Uniformity of tablet content testing done according to the procedure in FI IV, performed in the following way: pick no less than 30 units of tablets, 10 tablets were weighed individually and average weight calculated. Calculating the amount of active ingredient from each of 10 tablets of the results of the assay assuming the active substance is distributed homogeneously. Uniformity of dosage

requirements be met if the amount of active ingredient in each of 10 tablets were determined by means of the diversity of content lies between 85% - 115% of that indicated on the label, and the relative standard deviation of less than or equal to 6.0% (Ministry of Health Republic of Indonesia, 1995).

Bouyancy Evaluation

Buoyancy determined by measuring the tablet floating lag time and floating duration time. Determination procedure was performed as follows: tablet was put in a beaker containing 100 mL of 0.1N HCl buffer pH 1.2 with the testing temperature $37 \pm 0.5\ °C$. The time required to float towards the surface of the tablet is calculated as floating lag time and the total time is calculated as floating duration time. Testing was done by 5 tablets replication in each formula.

Dissolution testing

The study was undertaken by placing Diltiazem HCl tablet into a 900 mL dissolution medium, which was 0.1N HCl buffer pH 1.2, using USP type II apparatus (System 850 KS, Logan Instrument) at 50 rpm and 37±0.5°C. Sampling was performed during the 15, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes by taking 5.0 mL medium, filtering it, and pouring fresh 5.0 mL medium into the dissolution chamber. Absorbance was measured at λ 236 nm using a UV-Vis spectrophotometer (Genesys 10UV Scanning, Thermo Electron Scientific Instrument Corporation, USA). The concentration of drug realease was calculated (Indonesia Pharmacopeia, 1995). The dissolution efficiency was calculated at minute 720 (DE_{720}).

RESULTS AND DISCUSSION

Before being compressed to become tablets, the characteristics of homogenized powder were examined. The results can be seen in Table 2.

Table 2 Results of homogeneity testing

Formula	Levels of Active Ingredients (%)*	Coeficient of Variations (CV)
I	100.129 ± 0,248	4,962
II	101.223 ± 0,221	4,371
III	97.395 ± 0,202	4,155
IV	99.270 ± 0,220	4,440

*Data are presented as mean ± SD (n = 5)

Tablet friability of all formulas has a value of <1%. It meets the requirements. The lowest friability was in Formula II which has Carbopol at a high level. Similarly, the Formula IV also has a high level Carbopol tend to have less friability than Formula I and Formula III. This happens because the Carbopol has good compressibility and binding ability (Fayed, 2011).

Tablet Content Uniformity

Uniformity evaluation of Diltiazem Tablets showed in Table 3. Levels of diltiazem HCl in all formulas in the range of 90.0 to 110.0 % by value of CV < 6.0% , this indicate that tablets was met Indonesian Pharmacopeia requirement.

Table 3 Results of testing uniformity evaluation

Formula	Levels of Active Ingredients (%)	Coeficient of Variations (CV)
I	100.793 ± 3.386	3.359
II	102.340 ± 2.156	2.127
III	98.488 ± 2.860	2.904
IV	100.129 ± 2.676	2.673

Data are presented as mean ± SD (n = 10)

Bouyancy Evaluation Result

Evaluation of buoyancy observed was floating lag time (FLT) and floating duration time (FDT). Terms FLT used was 10-600 seconds in the hope tablet can float right in the stomach. Terms used FDT was not less than 12 hours. The buoyancy test results can be seen in Table 4. The response then processed using software Design Expert 8.0.7.1.

The analysis result of the FLT provides the equation:
Final Equations in Terms of Coded Factors :
$Y = 12.95$ to $5.15 * A - B + 5.05 * 7.85 * AB$
Final Equations in Terms of Actual Factors :
$Y = 71.667$ to $0.782 *$ ethyl cellulose - Carbopol + $0461 * 5815 *$ ethyl cellulose * Carbopol
Contour plots produced can be seen in Figure 1.

Table 4 Results of the evaluation of buoyancy tablet

Formula	Floating lag time (second)*	Floating duration time (hours)**
I	31,0±6,519	>12
II	5,2±0,447	>12
III	5,0±0	>12
IV	10,6±3,050	>12

*Data are presented as mean ± SD (n = 5)
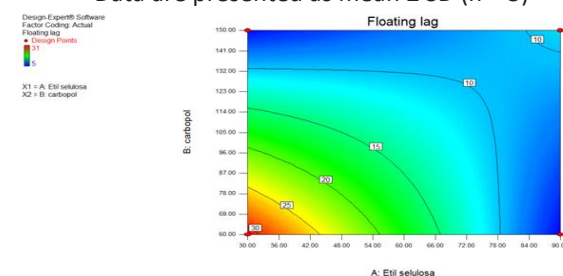**Data are presented as mean ± SD (n = 5)

Figure 1 Contour plot of Floating Lag Time

From the above equation is known that the use of polymers at high or low level capable of producing a response as desired. Contour plot produced can be seen in Figure 2 .
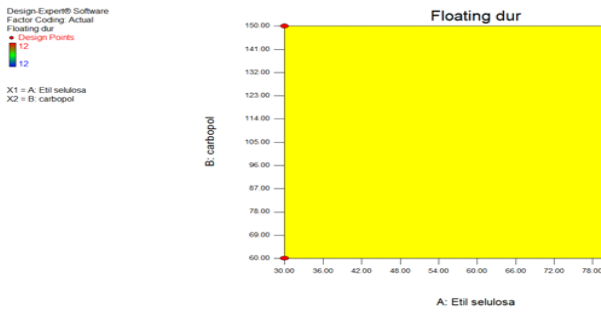
Figure 2 Contour plot of the Floating Duration Time

Figure 3 Contour plots response mucoadhesive strength

Mucoadhesive Strength Evaluation

The test results showed that mucoadhesive strength of Formula IV > Formula II > Formula I > Formula III. This shows that increasing level of polymer provides greater mucoadhesive strength. The test results are shown in Table 5.

Table 5 Results of mucoadhesive strength

Formula	Mucoadhesive Strength (g)*
I	89.067 ± 10.559
II	92.933 ± 13.564
III	80.867 ± 55.305
IV	112.467 ± 24.274

*Data are presented as mean ± SD (n = 5)

Mucoadhesive strength response was subsequently analyzed by Design Expert software 8.0.7.1. Mucoadhesive strength terms used was the response between 50-100 grams. The analysis produces the following equation:

Final Equations in Terms of Coded Factors:

Y = 93.83 + 2.83 * A + B + 8.87 * 6.93 * A * B

Final Equations in Terms of Actual Factors:

Y = 99.834 to 0.445 * ethyl cellulose - Carbopol + 0.111 * 5.136 * ethyl cellulose * Carbopol

The equation above shows that both polymers increase the response but the effect of Carbopol was more dominant. Carbopol is an anionic polymer with good ability of mucoadhesive. Contour plots produced can be seen in Figure 3.

Dissolution testing

Dissolution testing showed that only FI and FII is eligible slow-release preparations , which release the drug not less than 70 % for 12 hours(USPC, 2007). The results of dissolution testing is then made release profiles as shown in Figure 4 and release kinetics were analyzed using the equation of zero order, first order, Higuchi models, and Korsmeyer - Peppas models.
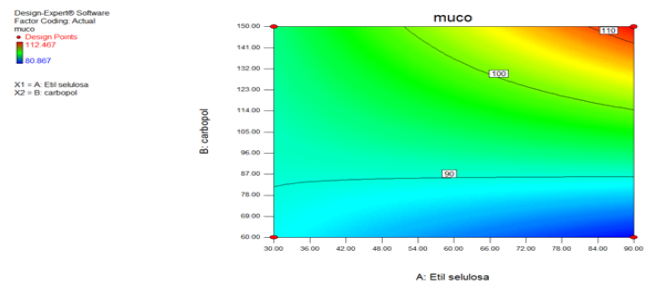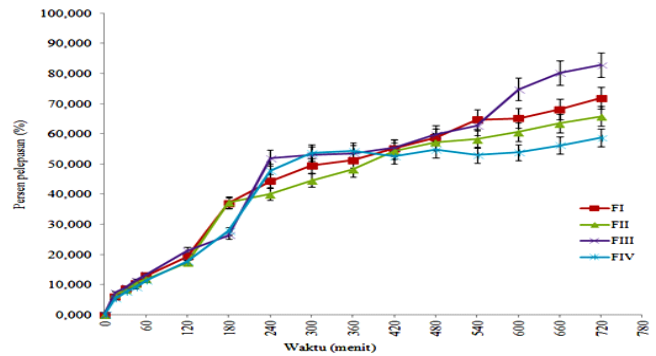

Figure 4 Kinetics of release of diltiazem HCl

The analysis showed that all formulas following the release kinetics Korsmeyer - Peppas models with value n = 0.731 FI , FII = 0.691 , FIII = 0.693 , and FIV = 0.789. All formulas follow the model release non Fickian transport (anomalous diffusion), which indicate that the rate of diffusion of drug was linear to polymer relaxation. N value also showed that the drug release mechanism controlled more than one process, diffusion and erosion. The release profile of diltiazem HCl Korsmeyer - Peppas models can be seen in Figure 5.
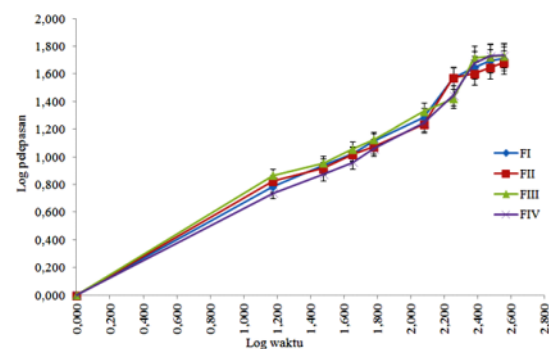

Figure 5 Kinetics release Korsmeyer - Peppas models

Based on the result of the release of each formula, dissolution efficiency at minute 720 (DE720) can be calculated. The requirements set are between 41.964 to 53.750 %. The test results indicate that all formulas meet these requirements. The test results can be seen in Table 6. These parameters were also analyzed using software Design Expert 8.0.7.1.

Table 6 Dissolusion Efficiency (DE$_{720}$)

Formula	DE$_{720}$(%)*
I	46.991 ± 1.429
II	44.000 ± 0.690
III	47.170 ± 1.069
IV	42.650 ± 1.303

*Data are presented as mean ± SD (n = 5)

The results of the analysis provide the equation:
Final Equations in Terms of Coded Factors:
Y = 45.20 to 0.29 * A - 1.88 * B - 0.38 * A * B
Final Equations in Terms of Actual Factors:
Y = 48.38583 + 0.019972 * Carbopol - ethylcellulose - 0.024739 * 2.83148 * ethylcellulose * Carbopol
The dominant factor lowers the response is Carbopol . Contour plots produced can be seen in Figure 6 .
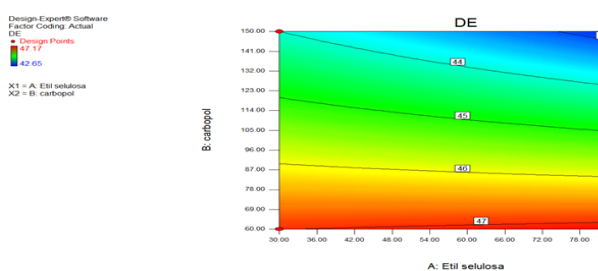

Figure 6 Contour plot of the response DE720

FLT response requirements chosen are between 10-600 seconds, the requirements of FDT chosen is more than 12 hours, the strength requirements mucoadhesive selected is 50-100 grams, and the requirements of the selected DE720 is 41.964 % - 53.750 %. The results of the analysis provide overlay plot as shown in Figure 7.
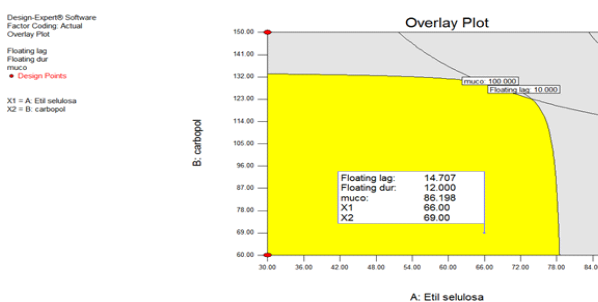

Figure 7 Overlay plot the optimum formula

The optimum formula which meets the requirements of the fourth response in the range between 60.0 mg Carbopol usage - 130.70 mg and the amount of ethyl cellulose is 30.0 mg to 77.15 mg. Predictions generated by this software is 33 points that satisfy the requirements of the desired response.

CONCLUSIONS

Based on research conducted, it can be concluded that the combination of Carbopol and ethyl cellulose were able to inhibit the release of the drug for more than 12 hours. This combination can also be used to extend the residence time tablet dosage form in the gastrointestinal tract so that the drug release can be controlled.

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