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The Effect of Polymers Ratio Carboxymethyl Chitosan, Polyvinyl Pyrolidone K-30, and Ethyl Cellulose N22 on Physico-Chemical Characteristics and Drug Release from Matrix Type Diclofenac Potassium Patch

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Abstract

Background*: Diclofenac potassium is an NSAID drug that is used in the treatment of mild to moderate pain. The use of this drug orally can cause side effects in the gastrointestinal tract, and the drug will undergo extensive first-pass metabolism in the liver. Therefore, preparations for transdermal patches were made.* ***Objective:*** *Determining the effect of the polymer ratios of carboxymethyl chitosan, polyvinyl pyrolidone K-30, and ethyl cellulose N22 on the physicochemical characteristics and drug release of a matrix type diclofenac potassium patch.* ***Methods****: In this study, matrix type diclofenac potassium patches were made using a combination of carboxymethyl chitosan (CMC), polyvinyl pyrrolidone (PVP) K-30 polymer, and ethyl cellulose (EC) N22 in a ratio of 2:3:7 and 3:2:7. Patches are made by mixing the entire polymer matrix and diclofenac potassium together, which are then evaporated and dried.* ***Results:*** *The results showed that the different polymer compositions of CMC, PVP K-30, and EC N22 resulted in patches with physicochemical characteristics that were not significantly different. The combination of these polymers is able to control the release of the drug from the patch for a long time. It was also found that increasing the concentration of CMC was able to increase the rate of release of diclofenac potassium. Formula 2 with a ratio of 3:2:7 is claimed to be the best formula in terms of physical, chemical, and drug release characteristics from the patch. Further studies are needed, such as drug penetration tests into the skin.*

Keywords*: transdermal patch, diclofenac potassium, carboxymethyl chitosan, polyvinyl pyrrolidone K-30, and ethyl cellulose N-22*

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INTRODUCTION

Diclofenac potassium is a phenylacetic acid derivative that belongs to the nonsteroidal anti-inflammatory drugs (NSAID) class of drugs. Diclofenac potassium has greater solubility and absorption than diclofenac sodium and is often recommended in the treatment of mild to moderate pain requiring a rapid onset of action. The drug's mechanism of action is as a non-selective cyclooxygenase (COX) inhibitor (Psimadas et al., 2012).

Oral use of diclofenac potassium can cause gastrointestinal side effects such as bleeding and peptic ulceration due to COX inhibition, which reduces prostaglandins in the gastric epithelium (Purnamasari et al., 2019). Diclofenac potassium has a short half-life of 1-3 hours and undergoes extensive first-pass metabolism in the liver that is only 50% of the systemically available oral dose (Rajabalaya et al., 2008).

Patches are transdermal dosage forms that deliver a specific dose of a drug into the bloodstream through the skin. The patch can release drugs slowly and steadily, with less change in drug levels than oral administration. It also avoids first-pass metabolism in the liver, keeps GI side effects to a minimum, and is easy for patients to use (Nalamachu and Gudin, 2020).

Transdermal patches are classified into two types: membrane patches and matrix patches. Matrix-type patches are thinner, lighter, and more flexible in the production process (Nalamachu and Gudin, 2020). Patch preparation is accomplished by thoroughly combining the active substances, polymers, and other components to be evaporated and dried.

Transdermal patches contain a drug, a polymer matrix, a penetration enhancer, adhesives, a backing layer, and additional excipients such as plasticizers (Al Hanbali et al., 2019). The drug crossing the skin process begins with drug release from the patch, followed by passive diffusion into the skin via the stratum corneum. Polymer is a crucial component of the patch since it influences and controls the rate of drug release from the patch (Nalamachu and Gudin, 2020).

Carboxymethyl chitosan (CMC) is a chitosan derivative that is hygroscopic, hydrophilic, has antibacterial activity, is biodegradable, biocompatible, non-toxic, has minimal immunogenicity, is affordable, and is easily accessible (Basmal et al., 2017 ; Shariatinia, 2018). Furthermore, CMC includes carboxymethyl groups, which may firmly bind water molecules via hydrogen bonds and improve their solubility in water, resulting in higher dissolution and bioavailability in the administration of drugs that are difficult to dissolve in water (Shariatinia, 2018). PVP is an amorphous synthetic polymer that is hygroscopic, non-toxic, and has a high swelling capacity. It also forms pores in the membrane that can aid release the drug from its base (Nurahmanto et al., 2018). Meanwhile, ethyl cellulose (EC) N-22 is a water-insoluble polymer that can maintain the drug in the preparation by generating a protective film (Nurahmanto et al., 2018).

The purpose of this study is to see how the combination of CMC, PVP K-30, and EC N-22 polymers in the ratios 2:3:7 and 3:2:7 affects the physicochemical properties and diclofenac potassium release from matrix type patches.

MATERIALS AND METHODS

Materials

Diclofenac potassium (obtained from PT. Dexa Medica), carboxymethyl chitosan (purchased from Xi'an Lyphar Biotech Co. Ltd), polyvinyl pyrrolidone K-30 (purchased from CV. Tristar Chemicals), ethyl cellulose N-22 (purchased from Dow Chemical Company), polyethylene glycol 400 (purchased from Indokemika Group), methyl methacrylate (purchased from Merck Schuchardt OHG), menthol, 96% ethanol and distilled water. The purity of the materials used was pharmaceutical grade.

Method

Preparation diclofenac potassium patch

The transdermal patch was prepared by mixing all the components of the material, consisting of the active ingredient, polymer, and other additives listed in Table 1. The manufacturing step begins with weighing each polymer in each formula. CMC was dissolved in 1.5 ml of aquadest, PVP K-30 was dissolved in 2 ml of 96% ethanol, and EC N-22 was dissolved in 2 ml of 96% ethanol. The three are stirred until homogeneous. Next, the PVP solution was mixed with the EC solution, and then the CMC solution was slowly added to the mixture and stirred at a constant speed until homogeneous. The next step is adding to the mixture a solution of menthol in 2 ml of 96% ethanol that has been mixed with diclofenac potassium. Then a total of 1.5 ml of PEG 400 was added to the mixed solution and stirred until homogeneous. Methyl methacrylate was also added to the mixture and stirred thoroughly. After all the mixing is complete, it is done overnight. The mixture is then poured into the mold with the inner diameter of the patch was 4 cm and the solvent evaporation process is carried out by placing it in a fume hood for 3 hours. Then it dried in an oven at 40 °C for 3 hours.

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Table 1. Formula of diclofenac potassium patch matrix type

Compound	Function	Quantity (mg)	
		Formula 1 (KPE= 2:3:7)	Formula 2 (KPE= 3:2:7)
Diclofenac potassium	Active ingredient	16.4	16.4
CMC	Polymer	80	120
PVP K-30	Polymer	120	80
EC N-22	Polymer	280	280
PEG 400	Plasticizer	1,695	1,695
Methyl methacrylate	Adhesive	48	48
Menthol	Enhancer	6	6

Note: KPE = CMC: PVP K-30: EC N-22
Total polymer weight = 480 mg
Surface area of patch = 12.56 cm^2

Evaluation of the patch

Organoleptic examination

Organoleptic examination of diclofenac potassium patch was carried out by visually observing the color, smell, and surface texture.

Weight uniformity

Weight variations were tested by individually weighing diclofenac potassium patches on an analytical balance and calculating the average weight. The weight of each patch should not deviate significantly from the average weight and %KV ≤ 6% (Patel *et al*., 2012).

Moisture content (MC)

The patches were weighed and kept at room temperature for 2.5 hours in a desiccator containing silica gel. The patch is then re-weighed to ascertain the preparation's moisture content. Percentage of moisture content can be calculated using the following formula:

$$\%\ Moisture\ content = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \text{ x } 100\%$$

Viscosity test

Acceptance requirements % moisture content of the patch are in the range of 2-10% (Shabbir et al., 2017).

Flatness

The flatness of the patch is determined by cutting the patch in the middle and two from each side of the patch with a size of 1x1 cm2. The length of the cut of each strip is measured before and after it is allowed to stand, and then the percent constriction is calculated using the formula:

$$\%\ \text{Constriction} = \frac{(L1-L2)}{L1} \text{ x } 100\%$$

Information:

L2 = End length of each strip

L1 = Initial length of each strip

The constriction acceptance value is 0%, which means it is equivalent to 100% patch flatness (Shekade, 2021).

Thickness

The thickness of the transdermal patch is tested by measuring the preparation with a caliper at different points of each preparation. The replication of the test was carried out three times ±SD.

Determination of drug content

The goal of surface morphology observation is to determine the surface structure and pores created on the surface patch. Scanning Electron Microscopy (SEM) (Hitachi FLEXSEM 1000) was used for this test with magnification 250X.

Surface morphology

The determination of diclofenac potassium level was carried out by dissolving the patch at 500 rpm for 30 minutes in 100 ml of solvent (a mixture of 96% ethanol and phosphate buffer pH 7.4±0.05 in a 3:7 ratio) and centrifuging at 3000 rpm for 15 minutes. Furthermore, the content of the drug was analyzed by UV spectrophotometry. Acceptance levels for drugs are in the range of 85–115% (Hendradi et al., 2019).

Homogeneity of drug content

The test was carried out by cutting the patch into four equal-sized parts. Each part was dissolved in 25 ml of solvent (a mixture of ethanol and phosphate buffer in a ratio of 3:7) and stirred at 500 rpm for 30 minutes. The samples were then centrifuged and analyzed with a UV spectrophotometer set to its maximum wavelength. Acceptance levels for drugs are in the range of 85–115% (Hendradi et al., 2019).

In vitro drug release test

The first step is to make a standard potassium diclofenac working solution in phosphate buffer pH.7.4 ± 0.05. Standard working solutions were made with levels of 2 ppm, 8 ppm, 10 ppm, 14 ppm, and 20 ppm. Each absorbance was observed using a UV spectrophotometer at the maximum wavelength. The maximum wavelength obtained is 277 nm. Then a standard curve of diclofenac potassium was made by connecting the concentration (x axis) vs. absorbance (y axis) of each standard solution of work and obtaining the

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linear equation y= ax+b. This equation can then be used to calculate the grade from the release test.

The release test was carried out in vitro with three replications of each formula. The test was performed with a USP-compliant dissolution apparatus, namely a 5-paddle over disk equipped with a diffusion cell and a paddle-type stirrer. Diffusion cells were used as a place for the transdermal patch to be placed before being closed by the cellophane membrane and then placed at the bottom of the vessel. A 500-mL phosphate buffer solution with a pH of 7.4 ±0.05 was used as the dissolution medium. The test temperature was kept constant at 37± 0.5 ºC, and the paddle speed was set to 50 rpm. Sampling was carried out at 0, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, and 420 minutes by taking 5 ml of sample. Each sampling was replaced with a new dissolution medium containing the same amount. The samples taken were analyzed for drug content by measuring the absorbance at the maximum wavelength using a UV spectrophotometer. The obtained levels are then corrected using the Wurster and Taylor equations with the following formula:

$$Cn = C'n + \frac{a}{b}\sum_{s-1}^{n-1} Cs$$

Note:
Cn = Actual levels after correction (ppm)
C'n = Readable levels (calculated from the sample absorption values read on the spectrophotometer) (ppm)
Cs = Levels read from the previous sample
a = Volume of sample taken
b = Volume of media

The cumulative amount of diclofenac potassium released from the basis of the unit area of the membrane each time (µg/cm^2) is obtained by calculating the concentration obtained each time (µg/mL) times the amount of media dissolution (ml) divided by the surface area of the patch (cm^2). Furthermore, the release profile of diclofenac potassium can be determined with data on the cumulative amount released.

The diclofenac potassium release rate (flux) is the slope (y) of the linear regression line equation of the diclofenac potassium release profile depicted when it reaches steady state.

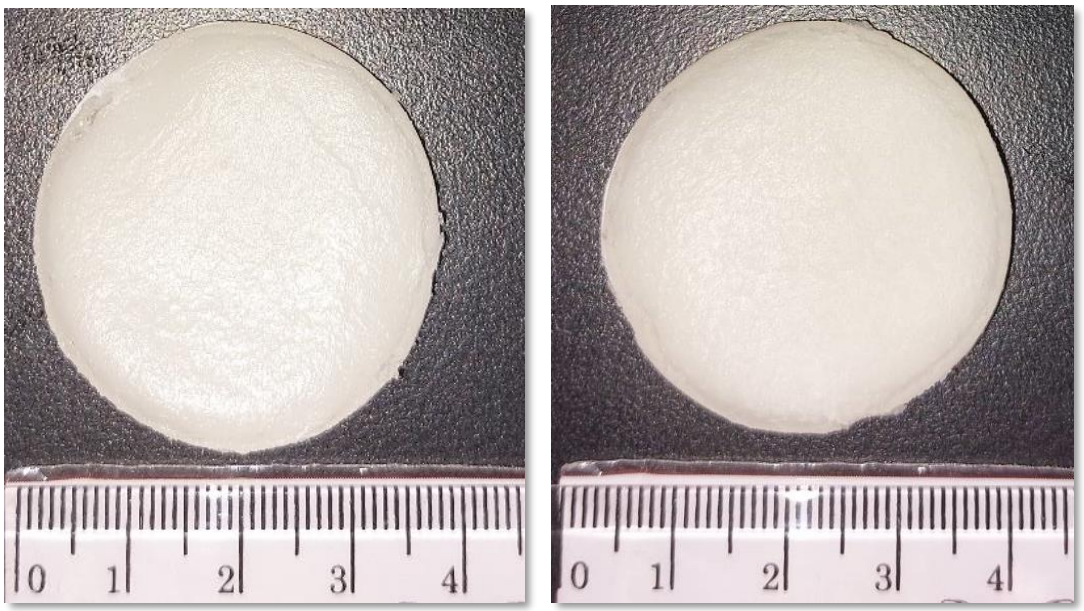
Data analysis

Data from the evaluation patch were analyzed using independent t-test with 95% confidence level or significance value (a) = 0.05. There is a significant difference symbolized by H_1, while the absence of a significant difference is symbolized as H_0. If the value of $a < 0.05$ is obtained, then H_1 is accepted.

RESULTS AND DISCUSSION

Organoleptic examination

Based on the results of organoleptic observations, formula 1 and formula 2 had the same visual appearance in terms of color, smell, texture, and patch. Patch is white, slightly smells of methyl methacrylate, has a smooth surface texture, is not brittle, and has a diameter of 4 cm. The results of the patch of the two formulas can be seen in Figure 1.



F1 F2

Figure 1. The visual appearance of patch in formulas 1 and 2 and the diameter of the preparation is 4 cm

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Table 2. Results of the of the physico-chemical characteristics of diclofenac potassium patch

Formula	Weight uniformity (gram)	Moisture content (%)	Flatness (%)	Thickness (cm)	Drug content (%)
F1	2.3110 ± 0.008	4.53 ± 0.12	100	0.245 ± 0.004	91.18 ± 0.99
F2	2.3308 ± 0.021	4.68 ± 0.11	100	0.247 ± 0.001	92.92 ± 0.57

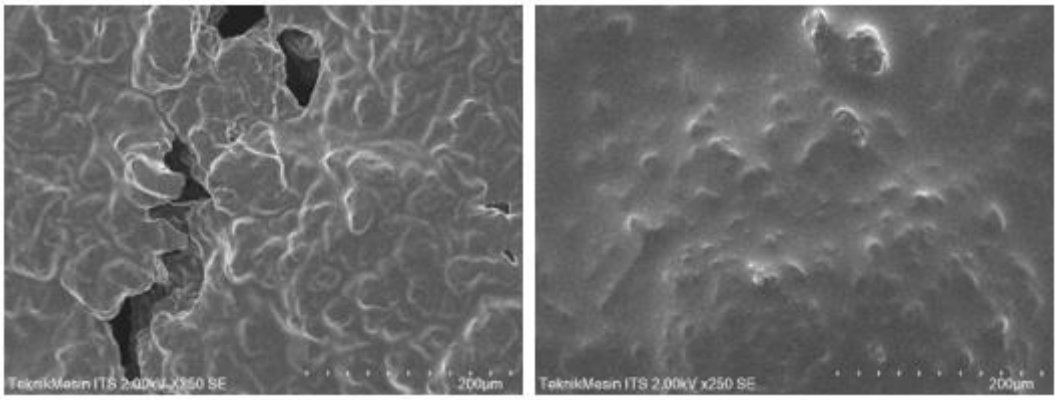

Figure 2. The surface morphology observation of diclofenac potassium patch using Scanning Electron Microscopy (SEM) (Hitachi FLEXSEM 1000) with magnification 250X

Table 3. Results of homogeneity drug content of diclofenac potassium patch

Formula	Part of the patch	Drug content (%)
F1	1	91.18 ± 0.75
	2	91.93 ± 0.37
	3	90.81 ± 0.99
F2	1	93.05 ± 1.12
	2	92.80 ± 0.94
	3	92.55 ± 0.57

The physico-chemical characteristics of the patch

The results of the evaluation of the The physico-chemical characteristics of the patch such as uniformity of weight, moisture content (MC), flatness, thickness, and drug content are presented in Table 2. Data is the average of 3 replications of the test ± SD. The % KV value of the two formulas in each evaluation has given a result of ≤ 6 % which indicates the uniformity of weight, MC, flatness, thickness, and drug content in both formulas. Tests for MC and drug levels in formula 1 and formula 2 also met the requirements, namely MC was in the range of 2-10%, while drug levels were in the range of 85-115% Hendradi et al., 2019 ; Shabbir et al., 2017). Statistical independent t-test each test has given a significance value of > 0.05, which means that there is no significant difference in weight, MC, flatness, thickness, and drug content between formulas 1 and 2. The result of the combination of carboxymethyl chitosan, polyvinyl pyrrolidone K-30, and ethyl cellulose N-22 2:3:7 and 3:2:7 on the characteristics still couldn't show the different characteristics. It takes a combination with a large difference between CMC and PVA to show the different characteristics.

Surface morphology

The transdermal patch was observed using a Scanning Electron Microscopy (SEM). Tests were carried out at 250x magnification. The results of surface morphology observation of diclofenac potassium patch can be seen in Figure 2.

In formula 1 and formula 2 transdermal patch, there have been scattered particles that blend together and are evenly distributed on the entire surface patch. It was also observed in formula 1 that visible pores were clearly visible on the surface of the patch. These pores are formed due to the higher amount of PVP K-30 polymer in formula 1. PVP K-30 has the ability to form pores on the membrane so that it affects drug release from the preparation (Franco and De Marco, 2020).

Homogeneity of drug content

The evaluation result of the homogeneity of drug content in patch are presented in Table 3. The homogeneity test aims to determine the uniform distribution of diclofenac potassium in each part of the

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patch. It is expected that if the drug is homogeneously distributed, the drug release can occur simultaneously in each part of the patch. The test results showed that the diclofenac potassium content in each patch met the requirements, which were in the range of 85-115% (Hendradi et al., 2019). Formula 1 and formula 2 also have a value of %KV ≤ 6%, which means that the drug content in each patch is uniform and is declared homogeneous. The result of statistical analysis independent t-test has given a significance value > 0.05, which means that there is no significant difference in diclofenac potassium content in each part of the patch between the two formulas.

In vitro drug release

The diclofenac potassium release test from the patch was carried out for 7 hours with a 5-paddle over disk apparatus.The results of the cumulative amount of diclofenac potassium released from the preparation at any time can be seen in Figure 3. The data is then used to determine the rate of drug release by connecting the cumulative amount of drug released (%) with the root of the time described when it reaches steady state. The release rate (flux) of diclofenac potassium is the slope of the linear regression equation on the curve. The release flux values in the two formulas are presented in Table 4.

In vitro drug release

The diclofenac potassium release test from the patch was carried

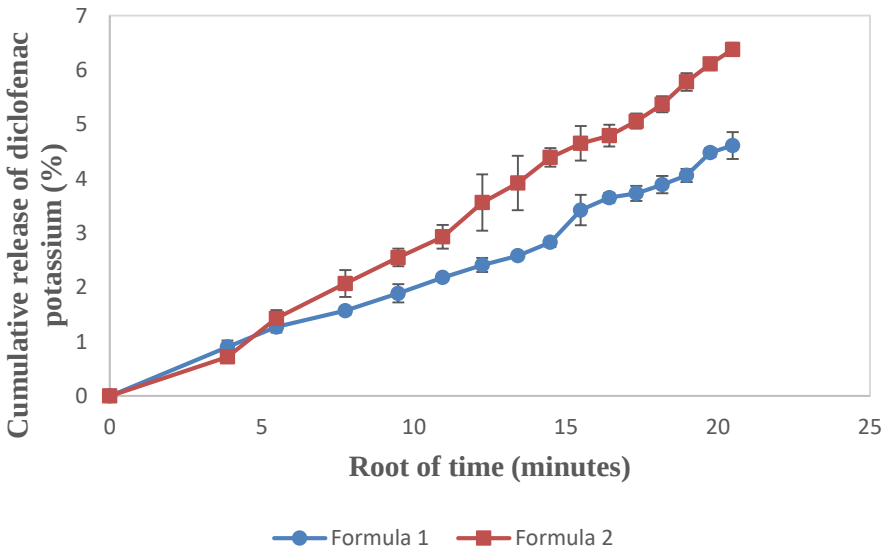

Figure 3. The curve of the cumulative amount of diclofenac potassium released in formulas 1 and 2. The data is the average of 3 replications ± SD

Table 4. Fluks of diclofenac potassium from patch

Formula	Fluks (µg/cm^2.minutes)
F1	0.2242 ± 0.0077
F2	0.3314 ± 0.0068

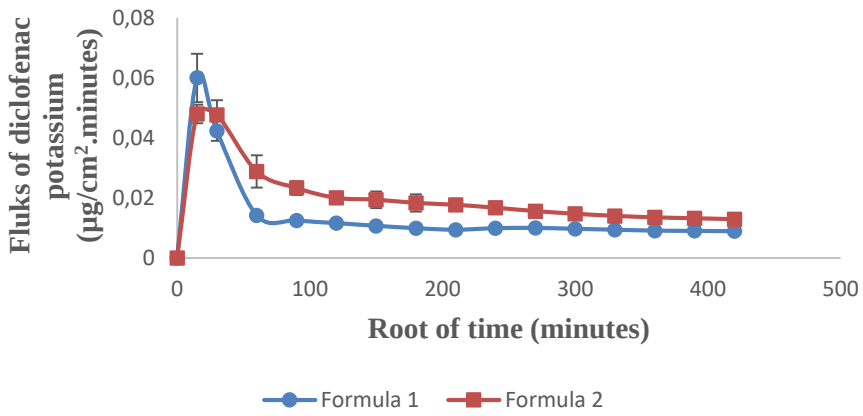

Figure 4. Controlled release curve of diclofenac potassium in formulas 1 and 2. Data is the mean of 3 replications ± SD

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Table 5. Regression equaltions and correlation coefficient values for each diclofenac potassium release kinetics model

Formula	Higuchi	Zero order	Korsmeyer-Peppas
F1	y = 0.2513x – 0.6062, R^2 = 0.9868	y = 0.0087x + 1.0818, R^2 = 0.9828	y = 0.5132x – 0.7072, R^2 = 0.9776
F2	y = 0.3299x – 0.5105, R^2 = 0.9952	y = 0.0116x + 1.651, R^2 = 0.9842	y = 0.572x – 0.7038, R^2 = 0.9935

According to Table 4, formula 2 produces a greater flux value than formula 1, which produces 0.3314 g/cm^2.min. The independent t-test resulted in a significance value < 0.05, indicating that there is a difference in the fluks value between the two formulations. The fluks of diclofenac potassium from patch grow as the number of CMC rises. CMC has excellent hydrophilic characteristics, which allow it to absorb and bind water firmly. The more bound water there is, the more the polymer swells, resulting in quicker drug release (Shabbir et al., 2018). When a result, as the number of CMC grows, so do the fluks of diclofenac potassium from the patch.

The release fluctuation data were then correlated with time to prove the controlled release of diclofenac potassium in both formulas. Figure 4 depicts the curve relationship of time vs. average fluctuations at each time. The results show that the release of diclofenac potassium from the patch in Formulas 1 and 2 occurred in a controlled manner from the 150th minute until the end of the test, namely the 420th minute. Controlled release is generally expected to occur in patches. This is due to the use of a combination of hydrophilic and hydrophobic polymers that are able to provide controlled drug release for a long time (Shivalingam et al., 2014).

Furthermore, the determination of the release kinetics of diclofenac potassium from the patch preparation was carried out. The diclofenac potassium release profile was aggregated using the Highuchi model, the Zero order, and the Korsmeyer-Peppas model. Table 5 lists the regression equations for each kinetic model. The results reveal that the release kinetics of diclofenac potassium from patch formulas 1 and 2 follow the Higuchi model, which is reflected by the coefficient of variation that is the greatest and closest to one. The Higuchi model is frequently applied to transdermal medicine administration devices such as patches (Paarakh et al., 2019). Diffusion is the primary drug release mechanism in the Higuchi model (Shabbir et al., 2018).

CONCLUSION

The combination of carboxymethyl chitosan (KMK) polymer, polyvinyl pyrrolidone (PVP) K-30, and ethyl cellulose (EC) N-22 in the ratios 2:3:7 and 3:2:7 resulted in a patch that met the physicochemical requirements and was capable of providing controlled release over a long period of time using the Higuchi model kinetics. The amount of carboxymethyl chitosan (CMC) added had no effect on the physicochemical properties of the two formulae developed. However, an increase in CMC has a considerable influence on the value of the drug release flux, which rises as well. So formula 2 with a 3:2:7 ratio of carboxymethyl chitosan (CMC) polymer, polyvinyl pyrrolidone (PVP) K-30, and ethyl cellulose (EC) N-22 yielded a greater diclofenac potassium release flux, specifically 0.3314 µg/cm^2.minute.

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