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Research Article

The combination of simplex lattice design and chemometrics in the formulation of green tea leaves as transdermal matrix patch

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Abstract

Aim: This study was aimed to formulate a transdermal matrix patch using green tea leaf extract.

Materials and methods: The transdermal matrix patch formulation was optimized by the simplex lattice design method. The correlation between responses was analyzed using chemometrics. The observed responses were: 1. the physical properties of the matrix patch, and 2. the percentage of dissolution efficiency of catechins, caffeine, and epigallocatechin gallate released from the patch. The determination of drug release kinetics was based on the curve-fitting analysis using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.

Results: The results showed that the optimal formula was obtained using the mixture of HPMC K100, HPMC K4M, and PEG 400 at a ratio of 4.0: 4.5: 0.5. The principal component analysis (PCA) showed that $\%DE_{300}$ values of catechin caffeine and epigallocatechin gallate positively correlate. A similar condition was observed between the weight and thickness of the matrix. Drug release kinetics follows the Korsmeyer-Peppas model.

Keywords

green tea, patch, transdermal, simplex lattice design, chemometrics

Introduction

Tea is a widely used beverage in worldwide (Michele et al. 2014; Setyawan et al. 2018a, b; Shiyan et al. 2019). Green tea has been reported to have antioxidant, antimutagenic, anticancer, antibacterial, antiobesity, antihypertensive, and antidiabetic properties (Batchelder et al. 2004; Geetha et al. 2004; Hsu 2005; Michele et al. 2014; Shiyan et al. 2020). Green tea contains many polyphenol compounds, such as catechins, which have been known to inhibit the process of initiation, promotion, and cancer progression (Bouzari et al. 2009). However, the oral bioavailability of catechin is very low (< 5%) (Baba et al. 2001). It also has a short elimination half-life, related to a fast systemic clearance (Hu et al. 2015). Epigallocatechin gallate (EGCG) also shows similar characteristics. Transdermal delivery, a method to administer drugs via the skin, can avoid problems related to the low oral bioavailability of many com-

pounds (Chen et al. 2011). Therefore, it is considered to be a promising alternative delivery route of catechin-related compounds (Lambert et al. 2006).

The transdermal delivery has been around for a long time, administered either in cream, ointment, and patch dosage forms. The transdermal delivery system has been designed to provide a controlled and continuous drug delivery through the skin into the systemic circulation in a non-invasive manner (Prabhakar et al. 2013; Kumar et al. 2015). The conventional drug dosage form provides a fluctuating plasma drug concentration, which might lead to toxicity, underdose, and low efficacy conditions. The objective of drug delivery is to improve the efficacy, ensure safety, and improve patient compliance. Transdermal delivery has many advantages. These include: 1) bypassing the first-pass metabolism, 2) providing a non-invasive delivery manner, 3) facilitating a comfortable and practical use, 4) allowing a long duration of therapy, 5) providing an easy dosing and easy stopping whenever required, and 6) improving patient compliance (Prausnitz and Langer 2009; Sachan and Bajpai 2013).

Several studies on the transdermal formulation of green tea extract have been reported (Batchelder et al. 2004; Perva-Uzunalić et al. 2006). However, none focused on the drug release kinetics. Furthermore, there were no studies combining the simplex lattice design and chemometrics for formula optimization. The optimization study using the simplex lattice design (SLD) allows profiling of the mixture's effect on the parameters. This method is useful for setting formulas, optimizing formula variables, determining the number of trials, and keeping the total formula concentration consistency. The experimental responses observed in this study were the patch matrix's physical properties and the percentage of dissolution efficiency of catechins, caffeine, and epigallocatechin gallate. The relationship of each response was analyzed using chemometrics of principal component analysis (PCA).

This analysis extensively applied the statistical and mathematical approach, mainly the multivariate methods. PCA is a relatively simple, nonparametric method for extracting relevant information from the dataset, identifying patterns in data, and expressing the data to highlight their similarities and differences (Singh et al. 2013; Moraes et al. 2016). In this study, PCA is used to analyze the correlation between responses such as physical properties of patch matrix (weight and thickness) and percentage of dissolution efficiency (%DE) of catechins, caffeine, and epigallocatechin gallate.

Based on the description above, this recent study was aimed: 1) to optimize the transdermal patch matrix formulation, 2) to estimate the effect of excipient (HPMC K4M, HPMC K100, and PEG 400) on the physical properties of patch matrix and %DE of catechins, caffeine, and epigallocatechin gallate, 3) to analyze the correlations of each experimental response, and 4) to determine a mathematical equation model of catechins, caffeine, and EGCG release.

Materials and methods

Materials and Instrumentation

Dried green tea (*Camellia sinensis* L.) Kuntze was harvested from Mitra Kerinci Farm in West Sumatra, Indonesia. HPMC K100, HPMC K4M, and PEG 400 (all are of pharmaceutical grade) were obtained as gifts from *Colorcon* Indonesia. Epigallocatechin gallate (EGCG), catechin, and caffeine (all are of analytical grade) were purchased from *Sigma-Aldrich*, Singapore.

Microbalance (*Radwag 2.3Y*), sonicator (*Transonic 570*), magnetic stirrer (*Stuart cb162*), pH meter (*Hanna HI 8314*), Franz cell diffusion (*Logan VTC 300*), HPLC (*Shimadzu 2010C HT*, Japan; equipped with an ultra-violet detector), and C18 column (150×4.6 mm, 5 µm, *Luna*, *Phenomenex*, USA) were used in this study.

Validation method

System suitability test (SST)

System suitability test (SST) was performed by injecting a mixture of standard solutions of catechin, caffeine, and EGCG with a concentration of 10 µg/mL. The parameters such as retention time, peak area, peak height, theoretical plate, tailing factor, resolution, and the high equivalent of the theoretical plate (HETP) were generated from each chromatogram. The selectivity was presented based on the resolution (Rs) values.

Linearity, the limit of detection (LoD), and limit of quantitation (LoQ)

A minimum of 5 concentrations series of the solution was prepared from the standard solutions of caffeine, catechins, and EGCG and then subjected to HPLC measurement. The responses were used to observe the value of the slope, intercept, and linear regression of the relationship curve between the content (x-axis) and the peak area of the chromatogram (y-axis). LoD and LoQ values were calculated based on the Signal to Noise ratio (S/N) of 3:1 and 10:1, respectively(Indrati et al. 2018; Shiyan et al. 2019).

Accuracy and precision

The accuracy was presented by the recovery percentage by analyzing three different series of analyte concentrations for six replications. Precision was determined as the standard deviation or relative standard deviation (RSD) values. In the critical method, it is generally accepted that the RSD must be less than the RSD determined by the Association of Official Analytical Chemists (AOAC).

Formula optimization

Formula optimization was performed by the simplex lattice design method (SLD) with the factors of HPMC K4M, HPMC K100, and PEG 400. This process was performed

by using *Design Expert ver. 7* software. Matrix weight, matrix thickness, dissolution efficiency values (%DE_{300}) of catechins, caffeine, and EGCG were used as the evaluated responses. The optimal formula was determined based on the criteria: 1) the smallest value of weight and thickness of the matrix; 2) the largest %DE_{300} values of gallic acid, catechin, caffeine, and EGCG. Parameter of %DE_{300} was calculated based on the area under the curve of the released compound from the matrix during 300 minutes. The determination of the released compound was performed by the RP-HPLC method.

Chemometrics

A chemometrics model is used to determine the correlation between observational responses. PCA models were implemented to evaluate the changes of the variable on each run. This process was performed by using *Minitab* software. PCA's output is a scree plot, score plot, loading plot, and a bi-plot graph describing the correlation and its effects on the principle components (PC).

Release kinetic study

Determination of the compound's release kinetics was carried out by the curve fitting analyses of the observation release curve based on the mathematical approaches, i.e., the zero-order, the first-order, Higuchi, and Korsmeyer-Peppas models (Costa and Lobo 2003).

Results and discussion

Method validation

The chromatogram is presented in Figure 1. The system suitability test (SST) result showed good results, as indicated by the analytical parameters provided in Table 1. The coefficient of variation (CV) for all parameter was less than 2%, CV of Resolution (Rs) of < 2%, tailing factor (< 2), and theoretical plates (N > 2000) (Snyder et al. 1997; Indrati et al. 2018; Setyawan et al. 2020).

Linearity, the limit of detection (LoD), and limit of quantitation (LoQ).

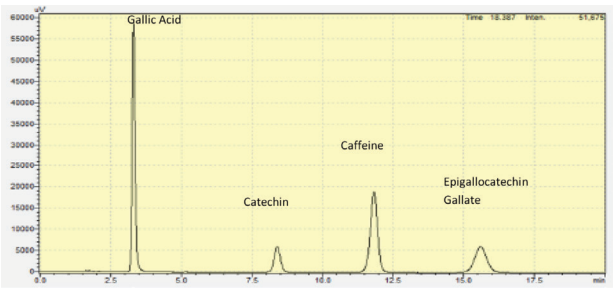

Figure 1. HPLC Chromatogram separation of EGCG, caffeine, and catechin (10 µg/mL) using mobile phase methanol-ortho phosphate-water (20:0.1:79.9 v/v/v) with flow rate 1 mL/min delivered isocratically and UV detected at λ 280 nm.

Table 1. HPLC system suitability test (SST) (n = 6).

	Ret. time	Area	Height	Theoretical plate	HETP	Tailling factor	Rs
				Catechin			
Mean	8.61	126629.83	8008.33	6972.66	21.51	1.02	17.37
SD	0.06	1731.61	46.48	6.73	0.02	0.00	0.04
CV	0.75	1.37	0.58	0.10	0.10	0.21	0.23
				Caffeine			
Mean	11.99	469797.33	25615.83	10143.39	14.79	0.99	7.58
SD	0.05	4746.09	237.69	17.79	0.03	0.00	0.12
CV	0.41	1.01	0.93	0.18	0.18	0.06	1.52
				EGCG			
Mean	16.19	250543.33	8061.17	6538.95	22.94	1.02	6.65
SD	0.16	3160.47	46.15	31.25	0.11	0.00	0.10
CV	1.02	1.26	0.57	0.48	0.48	0.37	1.57

The standard curves of dissolution studies were in the range of 0.05; 0.1; 0.2; 0.3; 0.4; 0.5 µg/mL with coefficient of correlation (r) was 0.9999 (catechin), 0.5; 1; 2; 3; 4; 5 µg/mL with (r) value was 0.9995 (caffeine), and 0.1; 0.2; 0.3; 0.4; 0.5; 1; 2; 3 µg/mL with (r) value was 0.9999 (EGCG). The results showed a good linearity in terms of the coefficient of correlation as illustrated in Figure 2. The limit of detection (LoD), and limit of quantitation (LoQ) values produced by catechin, caffeine, and EGCG were 0.007, 0.095, 0.026 µg/mL (LoD), and 0.024, 0.301, 0.086 µg/mL (LoQ), respectively.

Accuracy and precision

The accuracy and precision studies of drug release were performed by the standard addition method. The standard solutions were added into the matrix with three different concentrations with six replicates. A total of 0.1, 0.3, 0.4 µg/mL (catechin), 0.5, 1.0, 2.0 µg/mL (caffeine), 0.3, 0.5, 1.0 µg/mL (EGCG) were added into the matrix with the percentage of total recovery (intra-day) was 99.78% (CV 1.75%), 98.66% (CV 2.14%), 99.6% (CV 2.09%) for catechin, 105.86% (CV 1.44%), 100.13% (CV 3.14%), 103.52% (CV 0.64%) for caffeine, and

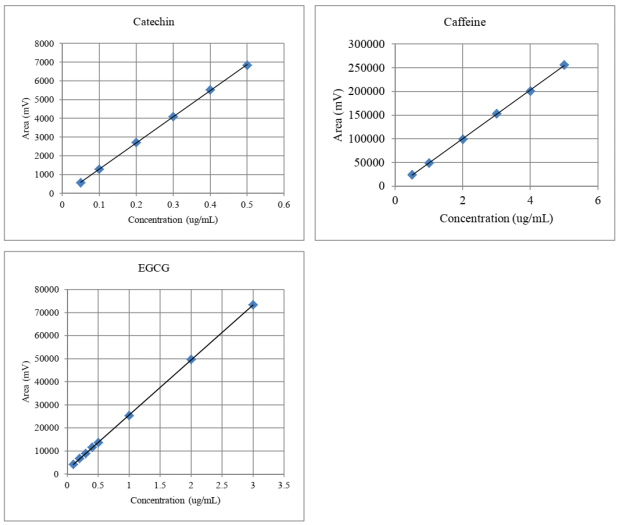

Figure 2. Standard calibration curve of catechin, caffeine, and EGCG for dissolution study.

101.99% (CV 2.61%), 98.89% (CV 2.94%), 101.81% (CV 1.64%) for EGCG. The results of the percentage of total recovery (inter-day) was 104.37, 97.87, 99.91% (catechin), 103.83, 105.54, 105.20% (caffeine), and 98.20, 102.28, 99.29% (EGCG). The results have fulfilled the requirements of AOAC guidelines. These facts indicated that this method is accurate and precise in determining the levels of the compounds dissolution or release study.

Formula optimization

The transdermal patch matrix was prepared using a solvent casting technique. The excipient composition was processed by the simplex lattice design (SLD) method with 13 runs (Table 2). The experimental results showed that matrix weight and thickness were 0.48–1.16 g and 0.10–0.33 mm, respectively. The $\%DE_{300}$ of catechin, caffeine, and EGCG were 15.22–47.83%, 21.92–53.47%, and 1.88–8.71%, respectively. The results showed that the $\%DE_{300}$ is all less than 90% over a period of 300 minutes. It can be caused by several things, such as the influence of dissolution media. The osmolarity of the dissolution medium contributed to auto-oxidation. Increasing the ionic strength at pH > 5 with the addition of sodium chloride will increase the rate of degradation of catechins and EGCG. EGCG is stable in acidic conditions (pH < 4). At a higher pH, it will trigger the EGCG epimerization process to become gallocatechin gallate (GCG). In addition, EGCG and catechin derivatives were able to interact with HPMC to form complex compounds that produce sediment or aggregates through hydrophobic interactions and hydrogen bonds. This complexation increased the stability of EGCG and catechins, but on the other hand, reduced the release of catechins and EGCG.

ANOVA analysis showed that all treatments generated a significant difference ($p < 0.05$). A mathematical equation describing the relationship between these components of the experimental response (matrix weight and matrix thickness) has followed a linear model (equations 1 and 2).

$$\text{Weight} = 0.63(A)+0.70(B)+1.17(C) \quad (1)$$

$$\text{Thickness} = 0.18(A)+0.22(B)+0.32(C) \quad (2)$$

Those equations demonstrate that all components play important roles in the increase in matrix weight and thickness. The PEG 400 (C) represents the most prominent role in increasing the weight of the matrix. PEG 400 might act as a plasticizer. Therefore its addition induced greater mobility of the polymer chains by replacing polymer-polymer interactions with polymer-plasticizer interactions. PEG 400 has non-volatile properties. The higher level of PEG 400 used in the matrix would make the matrix weight and thickness increase because PEG did not evaporate during the drying process.

ANOVA analysis showed that all treatments produced significant differences in the $\%DE_{300}$ values ($p < 0.05$). The special-cubic equation models appropriately describe the relationship between these components to the experimental response of $\%DE_{300}$ values of catechin, caffeine, and EGCG (equations 3, 4, and 5).

$$\%\text{DE300 catechin} = 32.04A+47.60B+41.99C-0.91AB+35.77AC-59.19BC-741.92ABC \quad (3)$$

$$\%\text{DE300 caffeine} = 40.29A+49.54B+47.86C+0.23AB+15.12AC-54.51BC-630.05ABC \quad (4)$$

$$\%\text{DE300 EGCG} = 6.18A+8.49B+6.78C-1.53AB+6.82AC-11.11BC-147.90ABC \quad (5)$$

Table 2. Formulation of green tea (1 g/mL) matrix patch transdermal by simplex lattice design (SLD) performed by Design Expert version 7.

Std	Comp. 1	Comp. 2	Comp. 3	Resp. 1	Resp. 2	Resp. 3	Resp. 4	Resp. 5
	A:hpmc k100	B:hpmc k4m	C:peg 400	Weight	Thick	DE Catechin	DE Caffeine	DE EGCG
	(mL)	(mL)	(mL)	(g)	(mm)	(%)	(%)	(%)
1	4.5	4	0.5	0.51	0.10	28.81	39.01	5.78
2	4.3	4.3	0.5	0.48	0.11	38.89	44.04	6.93
3	4.3	4	0.8	0.92	0.29	45.77	48.42	8.33
4	4	4.5	0.5	0.73	0.27	46.67	48.77	8.41
5	4	4.3	0.8	1.05	0.27	34.12	38.51	5.31
6	4	4	1	1.12	0.32	38.48	44.73	7.23
7	4.3	4.1	0.6	0.91	0.28	30.69	35.78	4.41
8	4.1	4.3	0.6	0.83	0.28	17.60	26.02	3.16
9	4.1	4.1	0.8	0.93	0.24	16.34	21.92	2.50
10	4.2	4.2	0.7	0.80	0.27	15.22	22.80	1.88
11	4.5	4	0.5	0.73	0.21	32.77	39.67	6.41
12	4	4.5	0.5	0.65	0.17	50.33	51.28	8.71
13	4	4	1	1.16	0.28	47.83	53.47	6.64

The HPMC K4M (B) represents the most prominent role in increasing the level of $\%DE_{300}$ of catechin, caffeine, and EGCG. The higher level of HPMC K4M used in the matrix would decrease the matrix viscosity and the diffusion layer to be quickly diffused out.

The optimum formula selection was determined by several criteria, namely the minimum weight and thickness of the matrix, the maximum of $\%DE_{300}$ of catechin, caffeine, and EGCG. The numerical approach showed that the optimal formula was at a ratio of HPMC K100 (A), HPMC K4M (B), PEG 400 (C) at 4.0: 4.5: 0.5. The contour plot diagram of the optimum formula is presented in Figure 3. The optimal formula estimated matrix weight, matrix thickness, $\%DE_{300}$ of catechin, $\%DE_{300}$ of caffeine, and $\%DE_{300}$ of EGCG at 0.67 g, 0.22 mm, 48.44, 49.68, 8.99%, respectively.

Chemometrics responses analysis

Principal component analysis (PCA) was carried out to determine the correlation of each response. PCA is an impor-

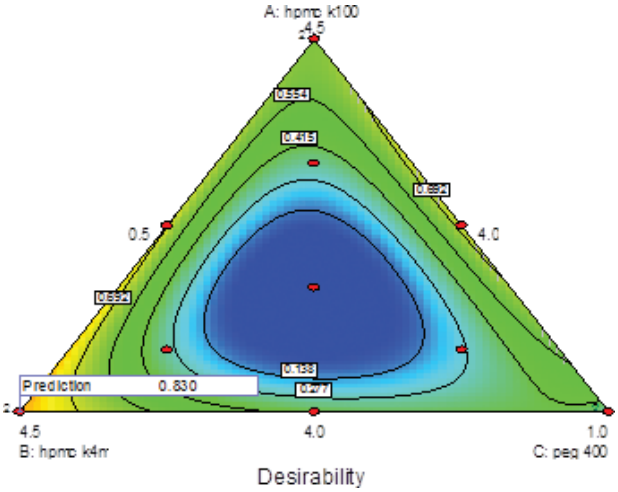

Figure 3. Contour plot diagram for optimum formula of transdermal matrix patch.

tant part of chemometrics and provides the most compact representation of all variations in the data table. PCA is designed to reduce complexity with a big dataset into a series of optimized and interpretable sizes. PCA finds out factors or principle components (PC_1, PC_2,…..PC_n), which are in linear combinations of the original variables describing each object (X_1, X_2,……X_n). If there are five variables or responses, there will be five principal components (PC). There are five parts of PCA, namely data, score, loading, and residual. The score of PCs is also called as hidden or latent variable. Samples that have the same scores of PC can be understood as the same object. The PCA process generated five factors or PC. Based on the scree plot graph in Figure 4a, only four PC were able to produce the data variation of 99.20%. The score plot graph in Figure 4b shows that the formula is divided into several quadrants with different distances from one another. Some formulas show similar response characters based on the proximity value of the PC value. For example, formula 8, 9, and 10 had proximity values of PC_1 and PC_2. It is illustrated that formula 8, 9, 10 had proximity of response character. The loading plot shows the strength of each variable affecting the PC. The angle between vectors describes how these variables correlate with one another. If two vectors form a narrow-angle, it indicates a positive correlation between the two variables, and if the vectors form an angle ≥ 90°, then they are not correlated or negatively correlated. The loading plot graph in Figure 4c showed that %DE of catechin, caffeine, and epigallocatechin gallate have a positive correlation. A similar correlation was also present between the weight and thickness of the matrix. In contrast, the matrix patch's physical properties have a negative correlation to the % DE of the compounds. PCA biplot graph in Figure 4d is merged a usual score plot with a loading plot (Rohman and Putri 2019).

Optimum formula verification

This verification was performed to ensure that the results predicted by the model did not differ significantly from the results of the observations. The number of experiments was replicated three times, and the data results are presented in Table 3. Verification results showed that there was no significant difference between the model-based prediction and the observation of each response ($p > 0.05$).

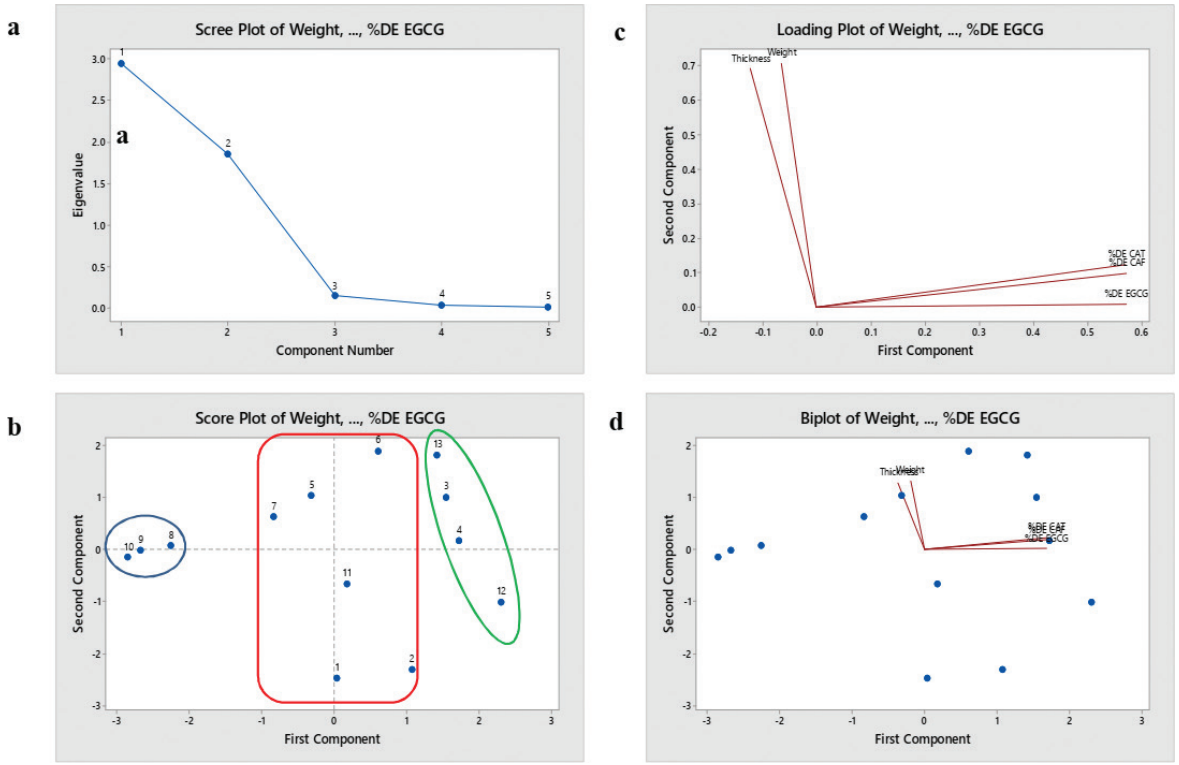

Figure 4. PCA scree plot illustrated the number of principal component to keep in PCA (**a**), PCA score plot illustrated the correlation between samples (formulas) (**b**), PCA loading plot illustrated the correlation between responses (**c**), PCA bi-plot (**d**).

Table 3. Verification of optimum formula (n = 3).

Sample (opt. Formula)	Weight	Thick	De Catechin	De Caffeine	De EGCG
	(g)	(mm)	(%)	(%)	(%)
HPMC K100:HPMC K4M:PEG 400 (4.0:4.5:0.5)	0.7	0.21	47.43	49.14	8.94
HPMC K100:HPMC K4M:PEG 400 (4.0:4.5:0.5)	0.68	0.22	48.41	49.5	8.74
HPMC K100:HPMC K4M:PEG 400 (4.0:4.5:0.5)	0.64	0.24	49.49	50.45	9.29
Mean	0.67	0.22	48.44	49.68	8.99
SD	0.03	0.01	1.03	0.68	0.28
CV	4.54	6.84	2.12	1.36	3.11
Model prediction	0.7	0.22	47.6	49.54	8.49
p-value	0.25	0.73	0.29	0.72	0.09

Release kinetics determination

The release profiles in Figure 5a were concluded that the kinetics of catechin, caffeine, and EGCG followed the Korsmeyer-Peppas (equation 6).

$$M/Mt^{\sim} = Kt^{n} \quad (6)$$

Where $M/Mt^{\sim}$ is a fraction of drug released at time t, k is the release rate constant, and n is the release exponent. The assessment is based on the value of the correlation coefficient (r) between the profile of the observed curve against the predicted curve. The value of $r \leq 1$ indicates a good correlation in both analyses. Based on the data results in Table 5, the release rate (k) of catechin, caffeine, and EGCG were 0.10–0.33 mg/hour, 0.23–0.51 mg/hour, and 0.01–0.08 mg/hour, respectively. The catechin, caffeine, and EGCG diffusion exponent value (n) were 0.29–1.11, 0.17–0.37, and 0.39–0.74, respectively. Based on the diffusion exponent value (n), the mechanism of catechin release (Fig. 5b) followed the Fickian diffusion (run 1, 2, 9, and 11), where the diffusion rate is less than relaxation. Some formulas follow non-Fickian diffusion (run 3, 4, 5, 6, 7, 8, 10, and 12) that the diffusion and the relaxation rate is balanced. Only run 13 followed the relaxation mechanism.

Caffeine release (Fig. 5b) followed a Fickian diffusion, in which the rate of diffusion is lower than the relaxation. Five formulas followed the Fickian diffusion (run 4, 8, 11, 12, and 13), while the remaining eight formulas followed non-Fickian diffusion. EGCG release (Fig. 5b) followed Fickian diffusion, where the rate of the diffusion is slower than the relaxation. Four formulas followed the Fickian diffusion (run 4, 8, 11, and 12), and the remaining nine formulas followed non-Fickian diffusion. The difference in this mechanism is related to the polymer composition. It has different physical and chemical properties, resulting in the polymer's water penetration

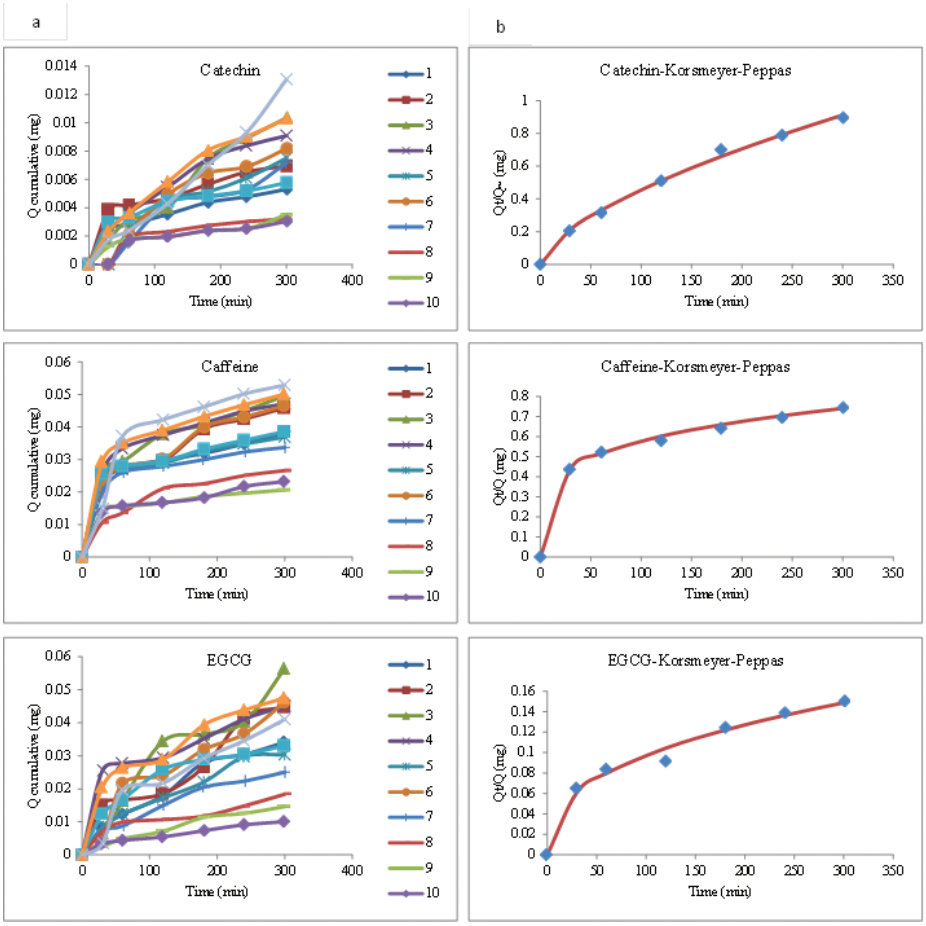

Figure 5. Dissolution profiles of caffeine, catechin, and EGCG from matrix patch transdermal for 300 minutes (**a**), Korsmeyer-Peppas fitting curve results (red lines) of catechin, caffeine, and EGCG drug release of the optimum formula (blue pattern) was performed by Solver (**b**).

Table 4. Coefficient correlation of fitting models between oberservation data and kinetic models.

Std	Catechin				Caffeine				EGCG			
	Coeff. correlation (r)											
	Zero order	First order	Higuchi	K-P	Zero order	First order	Higuchi	K-P	Zero order	First order	Higuchi	K-P
1	0.92	0.94	0.99	1.00	0.78	0.81	0.91	1.00	0.98	0.98	0.99	0.99
2	0.88	0.91	0.97	0.99	0.90	0.94	0.98	0.99	0.96	0.96	0.96	0.96
3	0.99	0.97	0.97	0.99	0.87	0.92	0.97	1.00	0.97	0.97	0.97	0.97
4	0.97	1.00	1.00	1.00	0.83	0.89	0.95	1.00	0.87	0.87	0.96	0.97
5	0.97	0.98	0.96	0.98	0.79	0.82	0.92	1.00	0.97	0.98	0.99	0.99
6	0.97	0.99	0.96	0.98	0.90	0.94	0.98	0.99	0.96	0.96	0.97	0.98
7	0.97	0.98	0.95	0.97	0.79	0.83	0.93	1.00	0.97	0.97	0.99	1.00
8	0.90	0.91	0.94	0.94	0.91	0.93	0.99	0.99	0.92	0.92	0.98	0.98
9	0.92	0.93	0.97	0.97	0.77	0.79	0.91	1.00	0.98	0.99	0.98	1.00
10	0.92	0.93	0.95	0.95	0.84	0.85	0.95	0.99	0.97	0.97	0.99	0.99
11	0.87	0.90	0.97	1.00	0.79	0.83	0.92	1.00	0.91	0.92	0.99	0.99
12	0.98	1.00	0.99	1.00	0.82	0.89	0.95	1.00	0.92	0.93	0.99	0.99
13	0.99	0.94	0.94	1.00	0.87	0.95	0.96	0.97	0.96	0.96	0.97	0.98

Table 5. Korsmeyer-Peppas constants of catechin, caffeine and EGCG.

Std	Constant of Korsmeyer-Peppas					
	Catechine		Caffeine		EGCG	
	k	n	k	n	k	n
1	0.27	0.35	0.42	0.17	0.05	0.55
2	0.37	0.29	0.40	0.33	0.06	0.57
3	0.24	0.82	0.46	0.28	0.06	0.57
4	0.32	0.58	0.48	0.24	0.07	0.43
5	0.19	0.79	0.40	0.18	0.06	0.74
6	0.20	0.81	0.41	0.33	0.06	0.59
7	0.15	0.86	0.36	0.20	0.05	0.61
8	0.12	0.57	0.22	0.39	0.03	0.40
9	0.16	0.41	0.23	0.17	0.01	0.72
10	0.10	0.62	0.23	0.24	0.01	0.53
11	0.31	0.30	0.42	0.18	0.05	0.49
12	0.33	0.63	0.51	0.23	0.08	0.39
13	0.18	1.11	0.45	0.37	0.05	0.59

leading to erosion. The dissolution medium's penetration caused the diffusion mechanism into the pores of the matrix produced by HPMC (hydrophilic polymer) and dissolving the compound. An increase in the volume of the medium caused the matrix expansion, followed by drug diffusion.

Conclusions

The results showed the optimal formula was obtained by a combination of HPMC K100: HPMC K4M: PEG 400 (4.0: 4.5: 0.5). The HPMC K4M represents the most prominent role in increasing the level of $\%DE_{300}$ of catechin, caffeine, and EGCG. The optimal formula produced weight, matrix thickness, %DE of catechin, caffeine, and EGCG were 0.67 g, 0.22 mm, 48.44, 49.68, 8.99%, respectively, with a desirability value of 0.830. The PCA showed that $\%DE_{300}$ catechin, $\%DE_{300}$ caffeine, and $\%DE_{300}$ epigallocatechin gallate have a positive correlation, as well as between the weight and thickness of the matrix. The drug release kinetics followed the Korsmeyer-Peppas model.

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