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Modeling of Solid-liquid Extraction of Total Phenolics from *Capsicum annium L.*

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Abstract: In this paper, the extraction kinetics of gallic acid equivalent of polyphenols from *Capsicum annium* was investigated. Ethanol was used as a solvent for extraction at different temperatures and the extraction medium was set at mixed and unmixed conditions to observe the changes in the kinetics. Two different strategies were applied for modeling. In the first one, four different models; namely Peleg, Mass Transfer, Logarithmic, and Page's Models were used for mathematically describing the physicochemical behavior of the extraction. The yields of extraction ranged from 1.39-3.27 mg/g depending on the extraction conditions. Mass transfer was found the best model representing the experimental data. Molecular and effective diffusivities were calculated. In the second strategy, extraction was modeled with the aid of response surface methodology. Extraction yield surface showed a linear relation with temperature, time, and solid-to-liquid ratio. The optimum conditions of extraction were 70°C, 90 minutes and 1/50 g/ml, and 3.29 mg/g gallic acid equivalent of total phenolics were extracted at those conditions. The model equations of this process could contribute to optimize the industrial extraction process and design of drug-delivery systems.

Keywords: Extraction; modeling; polyphenols; gallic acid; response surface methodology.

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INTRODUCTION

In recent years, several researchers have been focused on polyphenols in vegetables, fruits and herbs due to their contribution to human health. Phenolic compounds are capable of scavenging free radicals (1, 2), and are known as antioxidants (3). Gallic acid, quercetin, kaempferol and catechin are well known phenolics (4-6), and they have been used especially in cancer treatments (7, 8). One of the herbs containing gallic acid is *Capsicum annium L.* (red pepper) from Solanaceae family. It contains calcium, phosphorus, sodium, iron, B_1, B_3, C vitamins, lipids, carbohydrates, proteins, fibers and organic compounds producing its characteristic color (9). Researchers had been analyzed its phenolic content by HPLC analysis in detail (10, 11). The amount and the type of phenolic components in a plant material depend on not only genotype, maturation and growth conditions of the plant (12-14), but also the type and conditions of extraction.

The studies on extraction of phenolics from *Capsicum annium* focused on application of different type of solvents including pure methanol (15), methanol-water mixture (12, 16), pure ethanol (13, 14). In those papers, since they paid attention to the types of flavonoids in a plant, they analyzed the extracts after hydrolyzing them. When extraction temperature was increased up to 65^{o}C, the increase in the extraction yield was observed because of the increase in stability of phenolics due to non-enzymatic reactions (15).

All of the literature deals with the types of flavonoids in the plant, and there is scarce data on modeling of the extraction process of them. Mathematical modeling of the extraction is a useful engineering tool which facilitates the understanding, optimization, design and control of the processes with minimal time and energy consumption. There are two types in modeling of a process; namely mathematical models and Response Surface Methodology. Several equations have been proposed in the literature for mathematical modeling (17-20) and it seems that the best model differs due to the plant material and the extraction conditions. Response surface method is a combination of statistical and mathematical techniques used for analyzing several independent variables and also interactive effects among the variables on the response (21). This method has been used in several different optimizations including adsorption, extraction, fermentation etc. in an efficient manner (22-26). The advantages of the method are reduced number of experimental runs, cost and time (27, 9). In addition, the final equation found by this method can adaptable to any situation faced in the industry. There is not any research aiming to combine these two method for comparison within a special extraction case.

This study aimed to obtain a model equation by applying two procedures for optimization of extraction of phenolics from *Calendula officinalis*. Peleg's, Page's, mass transfer and logarithmic models were applied in mathematical modelling. The molecular and convective diffusion

coefficients were determined. In addition, response surfaces were constructed and the influences of temperature, solid-to-liquid ratio, and time on extraction yields were analyzed.

MATERIAL AND METHODS

Material

In the experiments of classical extraction, *Capsicum annium L.* was purchased from the herbalist has capable of growing this plant itself. Ethanol, Folin-Ciocalteu, and sodium carbonate were at analytical grade, and bought from Sigma-Aldrich.

Solvent extraction

Ethanolic extraction was realized batch-wise in a 250 mL Erlenmeyer flask. Extraction temperature, solid-to-liquid ratio, and mixing rate were chosen as the parameters of single- and multiple-parameter experimental designs. At the end of the specified extraction conditions the content of the flask was filtered through 110 mm filters (FilterLab) and filtered samples were used for total flavonoid analysis.

Determination of total phenolics

The concentrations of the total polyphenols in the extracts filtered were determined using the Folin-Ciocalteu method. In the analysis 0.4 ml of the extract was mixed with 5.1 ml of distilled water and 0.5 ml of Folin ciocalteu reagent. 1.5 ml of sodium carbonate solution (20% by weight) was added into the medium immediately and after mixing they kept in dark during two hours at room temperature. The color resulted from the colorimetric reaction between gallic acid in the sample and the Folin reagent was analyzed by UV-vis spectrophotometer (Perkin-Elmer) at 765 nm. The gallic acid equivalents (GAE) of total phenolics were calculated from the calibration curve (Absorbance = 0.01532 x Concentration (µg/ml); R^2=0.9989) and the results were expressed as mg GAE/g dry herb.

Extraction kinetics

Peleg's model: Since the extraction curves (concentration of phenolics vs. time) have similar shape with the sorption curves, all of the extraction processes could be described with a non-exponential equation of Peleg (17):

$$c_t = c_0 + \frac{1}{K_1 + K_2 t} \quad (1)$$

where c_t is the concentration of phenolics at time t (mg GAE/g), c_0 is the initial concentration of phenolics at time t=0 (i.e. c_0=0 in all experiments), t is the extraction time, K_1 is Peleg's rate constant (min.g/mg GAE), and K_2 is Peleg's capacity constant (g/mg GAE). In that equation, K_1 relates to the extraction rate (B_o) at the very beginning of the extraction ($t=t_0$):

$$B_0 = \frac{1}{K_1} \quad (\text{mg GAE/g}) \tag{2}$$

and K_2 relates equilibrium concentration (c_{eq}) at $t \to \infty$:

$$c_{eq} = \frac{1}{K_2} \quad (\text{mg GAE/g}) \tag{3}$$

Page's model: Another model used for the mathematical modeling of the extraction proposed by Page as follows (19):

$$c_t = \exp(-kt^n) \tag{4}$$

where k and n are the constants of Page's Model, and all the other parameters have the same definitions.

Logarithmic model: In mathematical modeling of extraction processes, Logarithmic model can also be used as follows:

$$c_t = a\,\text{Log}t + b \tag{5}$$

where a and b are the logarithmic model constants.

Mass transfer model: Extraction occurs through two steps; Firstly, the solvent penetrates into the solid to dissolve the extractable material, and then the extractable material diffuses from inside the solid to the bulk liquid. The rate determining step of the overall process is the diffusion (28). The rate of this step under unsteady-state conditions is defined by Fick's second law as:

$$\frac{\partial c}{\partial t} = D\,\frac{\partial^2 c}{\partial x^2} \tag{6}$$

where, c is the concentration of the solute (mg/g), t is time (min), D is the diffusion coefficient (m^2/min), and x is the distance of diffusion. This equation is valid when very dilute solution is used in the extraction and the diffusivity is assumed to be constant (29). If the shapes of the solid particles are assumed to as perfect spheres having the same properties and also if the perfect mixing of the solid-liquid medium occurs, the time of mass transfer at infinity, the general solution of this equation becomes:

$$\text{Ln}\left(\frac{c_\infty}{c_\infty - c}\right) = 0.498 + \frac{9.87Dt}{R^2} \tag{7}$$

where, c is the concentration of the extracted material in the solution at time t (mg/g), c_∞ is the concentration of the extracted material at time $t=\infty$, and R is the characteristic distance (m); i.e. for spheres it is equal to the radius. This equation can be rewritten as:

$$\text{Ln}\left(\frac{c_{eq}}{c_{eq} - c}\right) = a + K_{obs}t \tag{8}$$

Since c_∞ is considered as equilibrium concentration, a is a constant (0.498), and

$$K_{obs} = \frac{9.87D}{R^2} \quad (9)$$

In this research, Equation 8 was used to fit the experimental data and to obtain a, K_{obs} and diffusion coefficient values.

Validity of model prediction: The consistency between the predicted and experimental data evaluated by using the coefficient of determination (r^2), which is defined as:

$$r^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - y_{model})^2}{\sum_{i=1}^{n}(y_i - y_{mean})^2} \quad (10)$$

where, n is the number of samples, y_i is the actual experimental data of the ith sample, y_{model} is the model-fitting data of the ith sample, and y_{mean} is the mean value of all experimental data. A high r^2 value indicates high consistency between the fitted and experimental data.

Response surface methodology

In designing the experiments, firstly, the potential design factors of extractions, namely extraction temperature, solid-to-liquid ratio, time and mixing rate were studied to determine the most effective three parameters on the extraction yield by single-parameter procedure. It was found that mixing rate was not as effective as the other parameters (data not shown). Then, Box-Behnken design (BBD) was constructed for analysis of multi-parameter effects. The highest levels of respective parameters producing the highest yield were chosen as the center point values (coded as "0" in Table 1) of the optimization of the extraction, while the least and the highest values were used as minimum and maximum points (coded as "-1" and "+1" in Table 1), respectively. The chosen independent variables were coded according to (1).

Table 1. Levels and codes of experimental parameters used in Box-Behnken Design (BBD)

Parameters	-1	0	+1
x_1: Temperature (°C)	30	50	70
x_2: Time (min)	30	60	90
x_3: Solid/liquid (g/mL)	1/30	1/40	1/50

$$x_i = \frac{x_i - x_0}{\Delta x} \quad (11)$$

where x_i is the dimensionless coded value of ith independent variable, x_0 is the value of x_i at the center point, and Δx is the step change value. The behavior of the system is explained by the following second-order polynomial model:

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i=1}^{k-1} \sum_{j=2}^{k} \beta_{ij} x_i x_j + \epsilon \quad (12)$$

where Y is the predicted response, x_i, x_j,...,x_k are input variables, which affect the response Y, x_i^2, x_j^2,...,x_k^2 are the square effects, β_0 is the intercept term, $x_i x_j$, $x_j x_k$ and $x_i x_k$ are the interaction effects, β_i (i = 1, 2, . . . , k) is the linear effect, β_{ii} (i = 1, 2, . . . , k) is the squared effect, β_{ij} (i = 1, 2, . . . , k) is the interaction effect, and ε is the random error (30-31).

The Design-Expert 9.0 (Stat-Ease Inc., Minneapolis, MN, USA) software was used for regression and graphical analysis of the experimental data to fit the equations developed. Design of fifteen experiments consisting of three replicates at the central point was fitted into a polynomial model. The optimum values of the selected variables were obtained by solving the regression equation in which desired values of the process responses were set as the optimization criteria.

RESULTS AND DISCUSSION

The aim of the present study was to determine the mathematical equation fitting to the experimental results of batch extraction yields. Two different optimization methods were applied to reach this aim by plotting the values of gallic acid equivalent of total phenolics extracted versus time for different extraction conditions. In the first approach, four different mathematical relations defining the physicochemical behavior of extraction were chosen; i.e.; Peleg's, Mass transfer, Logarithmic, and Page's equations. The models were statistically analyzed and compared with their respective determination of coefficient (r^2) value. The constants of respective models and their r^2 values were summarized in Table 2.

As it can be seen from Table 2, Peleg's model was not as successful as other methods applied. Mass transfer model produced the highest value of determination of coefficient and the a-values were close to its exact value of 0.498. Although, values of determination of coefficient in mass transfer, logarithmic and Page's models were all acceptable, it seemed that logarithmic model caused more reliable results than the others because it produced nearly the same values for regression coefficients under different extraction conditions. In the literature, different models were found as the best model on the kinetic analysis of extraction depending on the different plants and extractable materials (19, 32-34). It is impossible to compare the kinetic results of this research with the one in the literature that focused on the extraction of total phenolics from *Capsicum annium* since there is not any research focusing on it.

Table 2. Model parameters of extraction kinetics

Peleg's model			
	K_1	**K_2**	**r^2**
70°C-molecular	3.0392	0.3048	0.8414
70°C-convective	1.1899	0.326	0.7463
Mass transfer model			
	K_{obs}	**A**	**r^2**
70°C-molecular	0.0361	0.4247	0.9804
70°C-convective	0.0370	0.5534	0.9187
Logarithmic model			
	A	**b**	**r^2**
70°C-molecular	1.2769	0.5614	0.9662
70°C-convective	1.1163	1.0375	0.9146
Page's model			
	K	**n**	**r^2**
70°C-molecular	0.2338	0.3723	0.9704
70°C-convective	0.4461	0.2227	0.9723

In the detailed analyses of the models, results were employed by plotting the calculated values of concentrations for each model and their respective experimental values (Figures 1-8) vs. time. As it was expected from its lower r^2 value, high discrepancies between concentrations estimated by Peleg's equation and experimental data were observed in both molecular (unmixed extraction medium; Figure 1) and convective extractions (mixed extraction medium; Figure 2). Comparing the other three models, the excellent fitness between the experimental data obtained under unmixed extraction medium conditions at 70°C and estimated concentrations of phenolics were obtained by mass transfer model (Figure 3). Either in logarithmic or Page's model equations caused less (especially in logarithmic model; Figures 5 and 6) or higher estimated values under all conditions (Figures 7 and 8). Figures clearly showed that, extraction yield increases rapidly at the beginning of extraction due to high driving force (concentration difference between solid and solvent), and that this increase getting lesser as the time passes due to decrease in driving force. In each case, extraction was reached equilibrium at the end. This behavior is explained by the mass transfer model appropriately. From Equation 9, the molecular and convective diffusion coefficients were calculated as $2.67.10^{-10}$ m^2/s and $2.73.10^{-10}$ m^2/s by using the average diameter of the particle size of 0.27 mm, respectively. According to the results, a 2.2% increase of diffusion coefficient with mixing was observed. This result was in accordance with the single-parameter effect analysis in which mixing rate was found less effective than the other parameters on extraction yield. In addition, the yields were determined as 3.11 mg GAE/g and 3.27 mg/GAE for molecular and convective extractions, respectively. As a result, the increase in diffusion coefficient yielded nearly 5% increases in extraction.

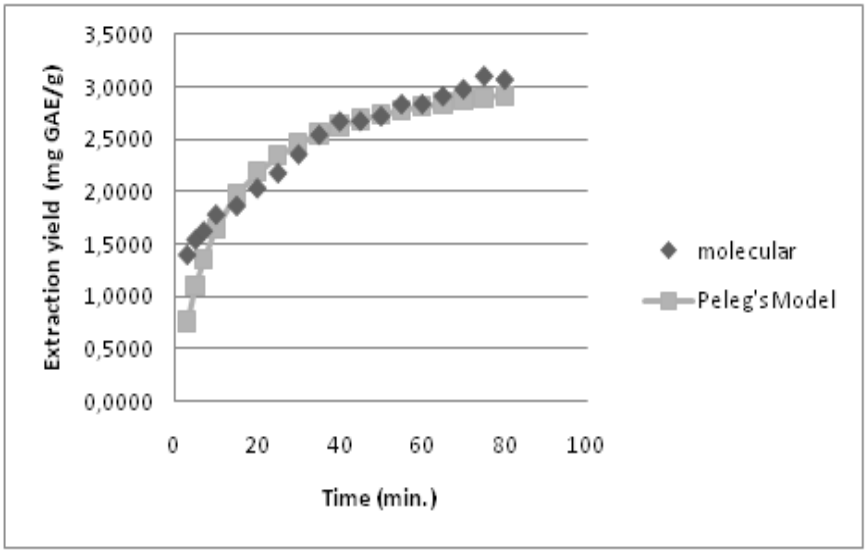

Figure 1. Experimental data obtained at 70°C under unmixed extraction medium fitted to Peleg's Model.

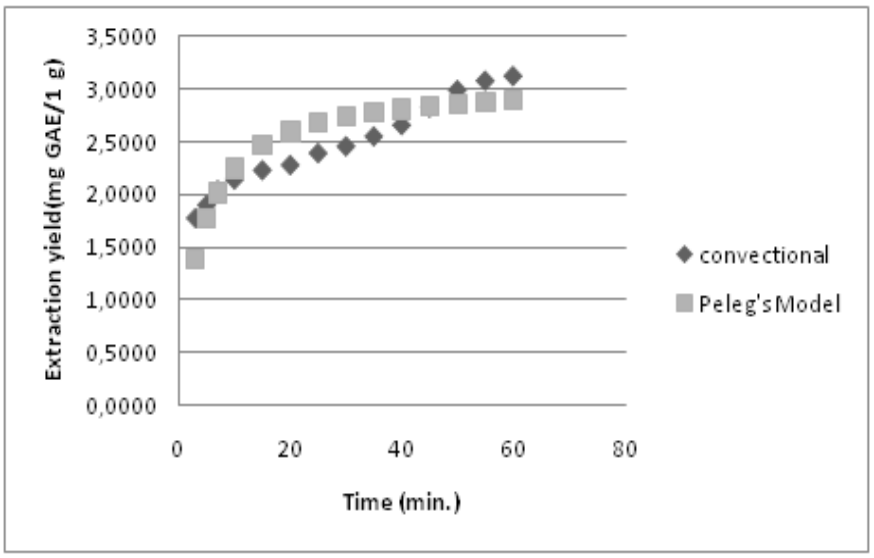

Figure 2. Experimental data obtained at 70°C under mixed extraction medium fitted to Peleg's Model.

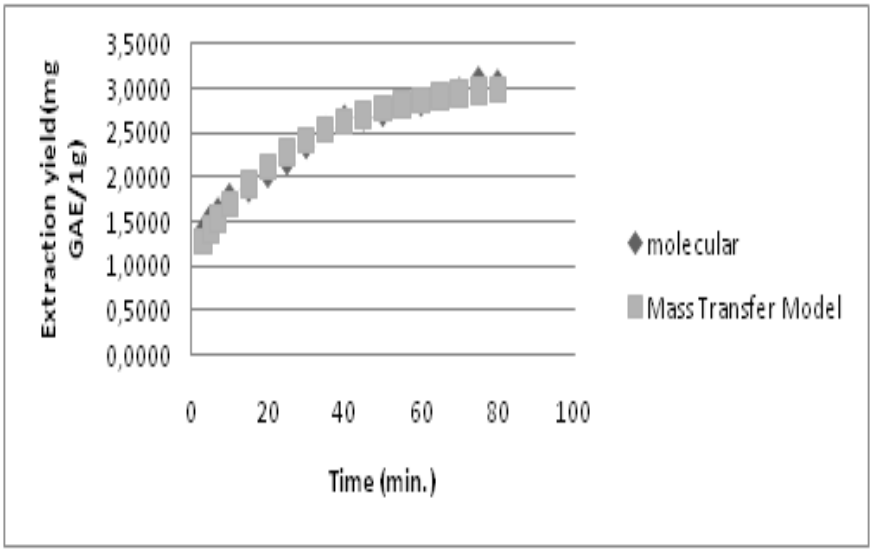

Figure 3. Experimental data obtained at 70°C under unmixed extraction medium fitted to Mass Transfer Model.

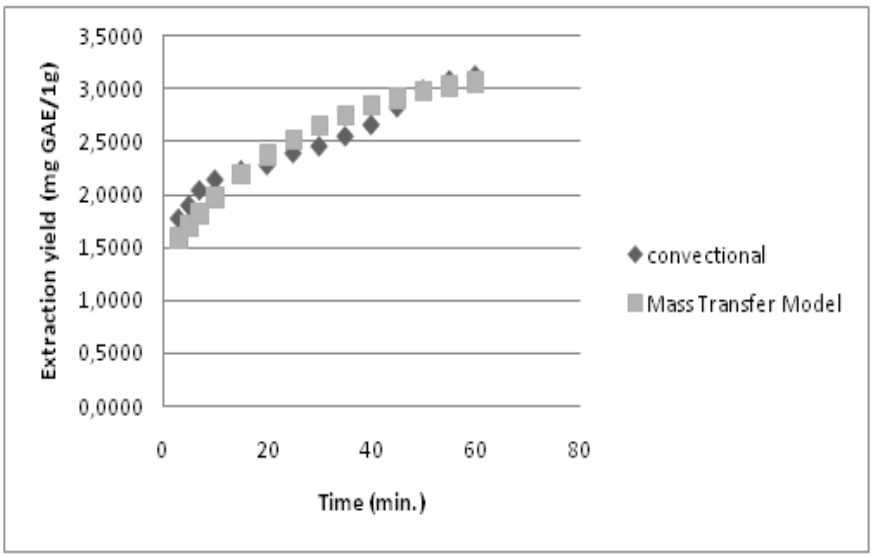

Figure 4. Experimental data obtained at 70°C under mixed extraction medium fitted to Mass Transfer Model.

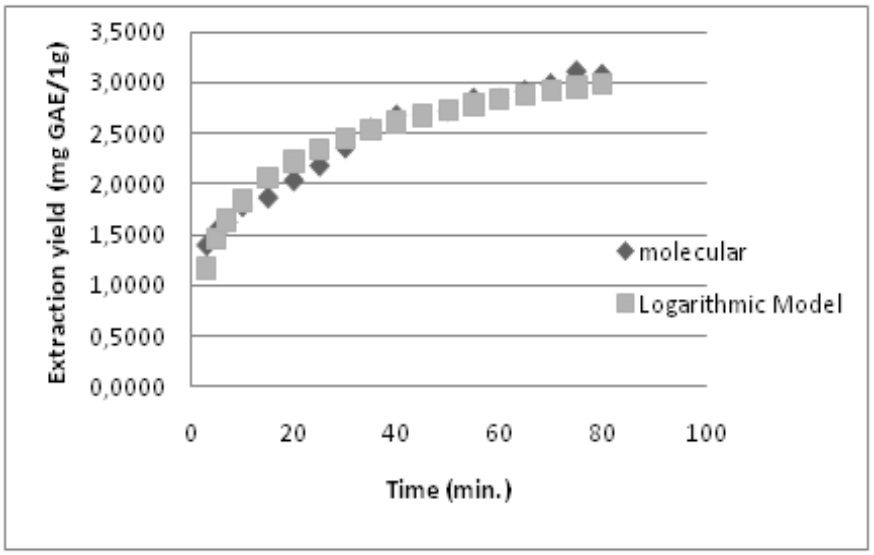

Figure 5. Experimental data obtained at 70°C under unmixed extraction medium fitted to Logarithmic Model.

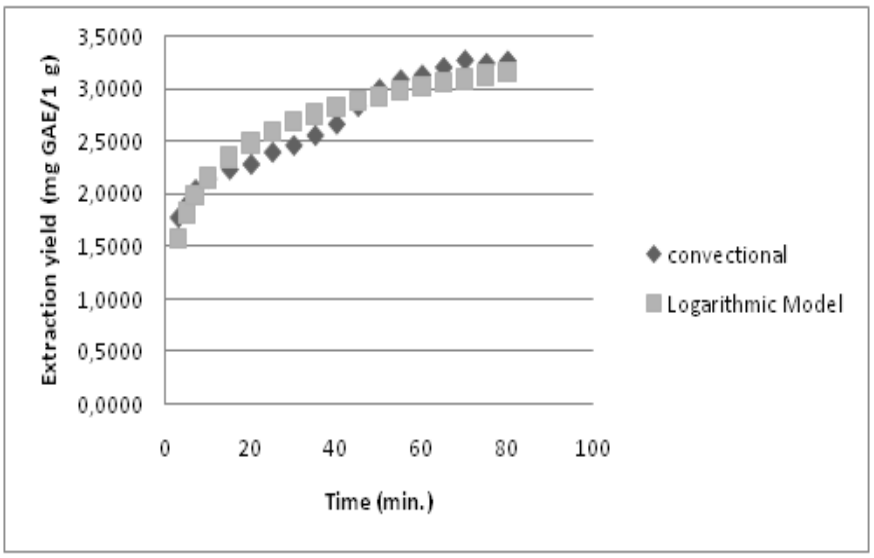

Figure 6. Experimental data obtained at 70°C under mixed extraction medium fitted to Logarithmic Model.

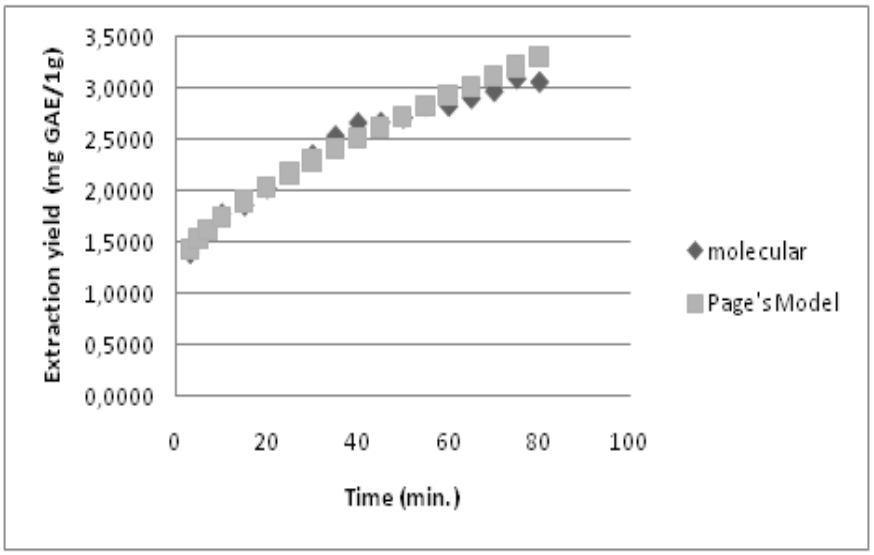

Figure 7. Experimental data obtained at 70°C under unmixed extraction medium fitted to Page's Model.

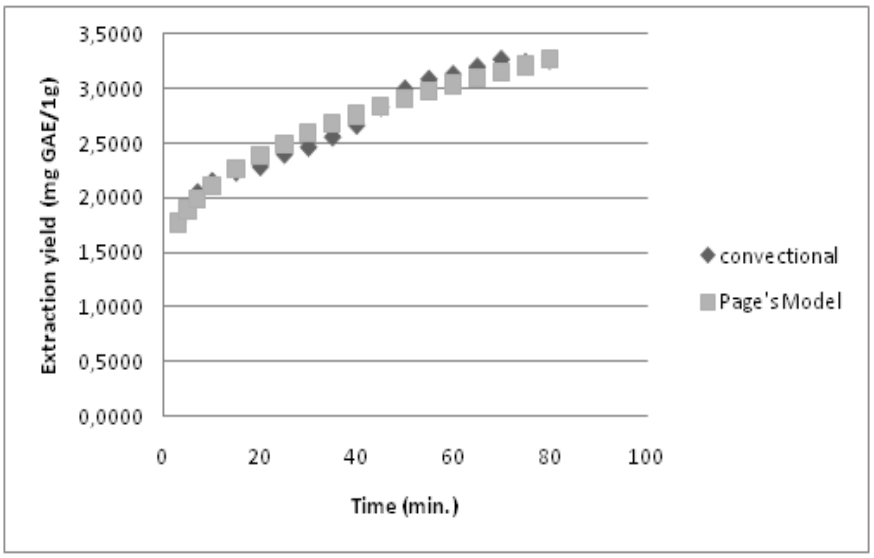

Figure 8. Experimental data obtained at 70°C under mixed extraction medium fitted to Page's Model.

In the second procedure of optimization of extraction, three-parameter three-level Box-Behnken design applied within response surface methodology. In the study, the calculated values of gallic acid equivalents of phenolics (Table 3) at respective conditions were entered into the Design-Expert 9.0 software. In the experiments the yield of extraction ranged from 1.45 to 3.30 mg GAE/g depending on the extraction conditions. The standard deviation of experimental results at the center points was 2.2%. All of the suggested functions were investigated by applying statistical analysis of the program, and the linear model was found to be the best function (Table 4) representing the extraction surface of the total polyphenols from *Capsicum annium*. In this decision, the highest regression coefficient (R^2= 0.9834), and the highest fitness in between the experimental data (actual) and their respective calculated values of the function (predicted) were

considered (Figure 9). The symmetrical relationship between them (Figure 9) approved the applicability of the function chosen. Generally, second order polynomials found the most appropriate functions when response surface methodology was applied to the systems (28-29). This observation results from the interrelation of parameters on the process response. In this study, the interactive effects between parameters were so low that the linear relations were found as enough for presentation of the extraction surface. This was approved by the statistical analysis of software function in which showing the model as "significant", and lack of fit as "insignificant" (Table 4). The larger the F value and the smaller the p value, the higher the effect of the parameter on the extraction of the flavonoids of this plant. So, the dominant parameter was determined as temperature, whereas the least effective parameter was solid-to-liquid ratio. This result showed that at the extraction conditions, liquid had capable of dissolving all of the phenolic compounds in the solid.

At this point, three-dimensional response surfaces were constructed in this study by using software. The interactive effects of the parameters were shown in Figures 10-12. In those, red regions shows the highest amount of total flavonoids extracted, yellow and blue parts represent the lower and much lower extraction yields than those. As it can be seen from figures, extraction temperature must be in the coded range of [0.5;1] for the highest flavonoid extraction.

Table 3. Experimental design and yields of extraction

No	x_1	x_2	x_3	Amount of gallic acid (mg/100g)
1	-1	-1	0	145,175
2	1	-1	0	291,206
3	-1	1	0	166,080
4	1	1	0	330,475
5	-1	0	-1	150,299
6	1	0	-1	289,531
7	-1	0	1	167,194
8	1	0	1	304,941
9	0	-1	-1	209,034
10	0	1	-1	241,636
11	0	-1	1	215,123
12	0	1	1	254,214
13	0	0	0	248,468
14	0	0	0	238,997
15	0	0	0	242,102

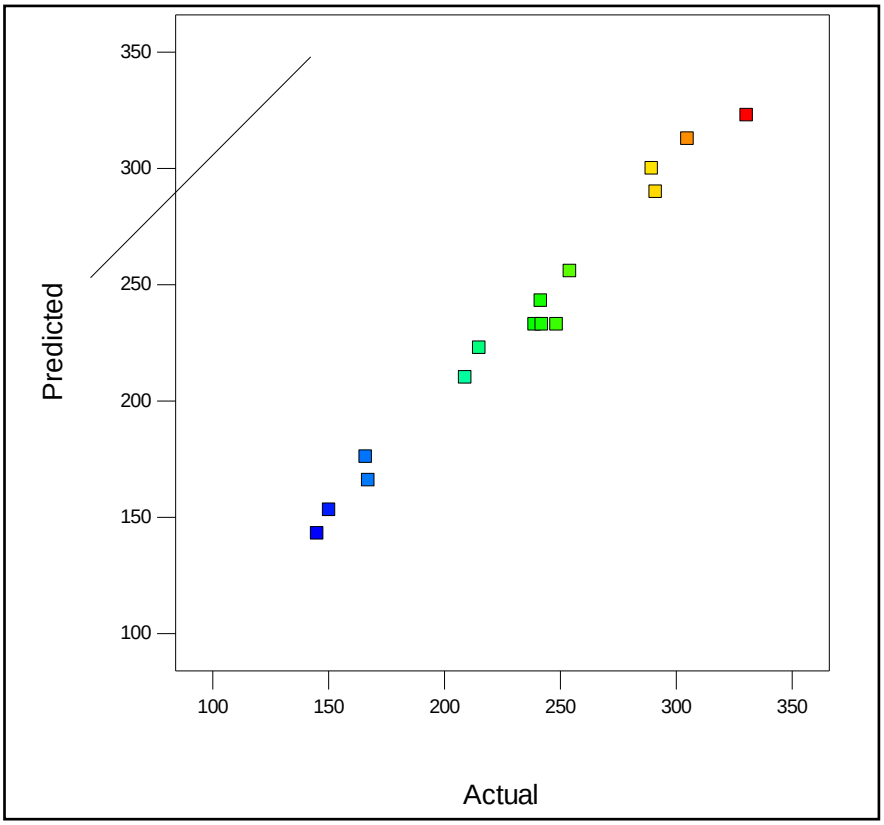

Figure 9. Experimental results and extimated values of linear function of response surface model.

Table 4. ANOVA table

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	45629,32	3	15209,77	217,39	< 0.0001
A-Temperature	43130,87	1	43130,87	616,45	< 0.0001
B-Time	2173,68	1	2173,68	31,07	0,0002
C-Solid/liquid	324,77	1	324,77	4,64	0,0542
Residual	769,63	11	69,97		
Lack of Fit	723,01	9	80,33	3,45	0,2451
Pure Error	46,62	2	23,31		
Core Total	46398,95	14			

Model: Significant; Lack of fit: Not significant; R-Squared: 0.9834; Adjusted R-Squared: 0.9789; Predicted R-Squared: 0.9722

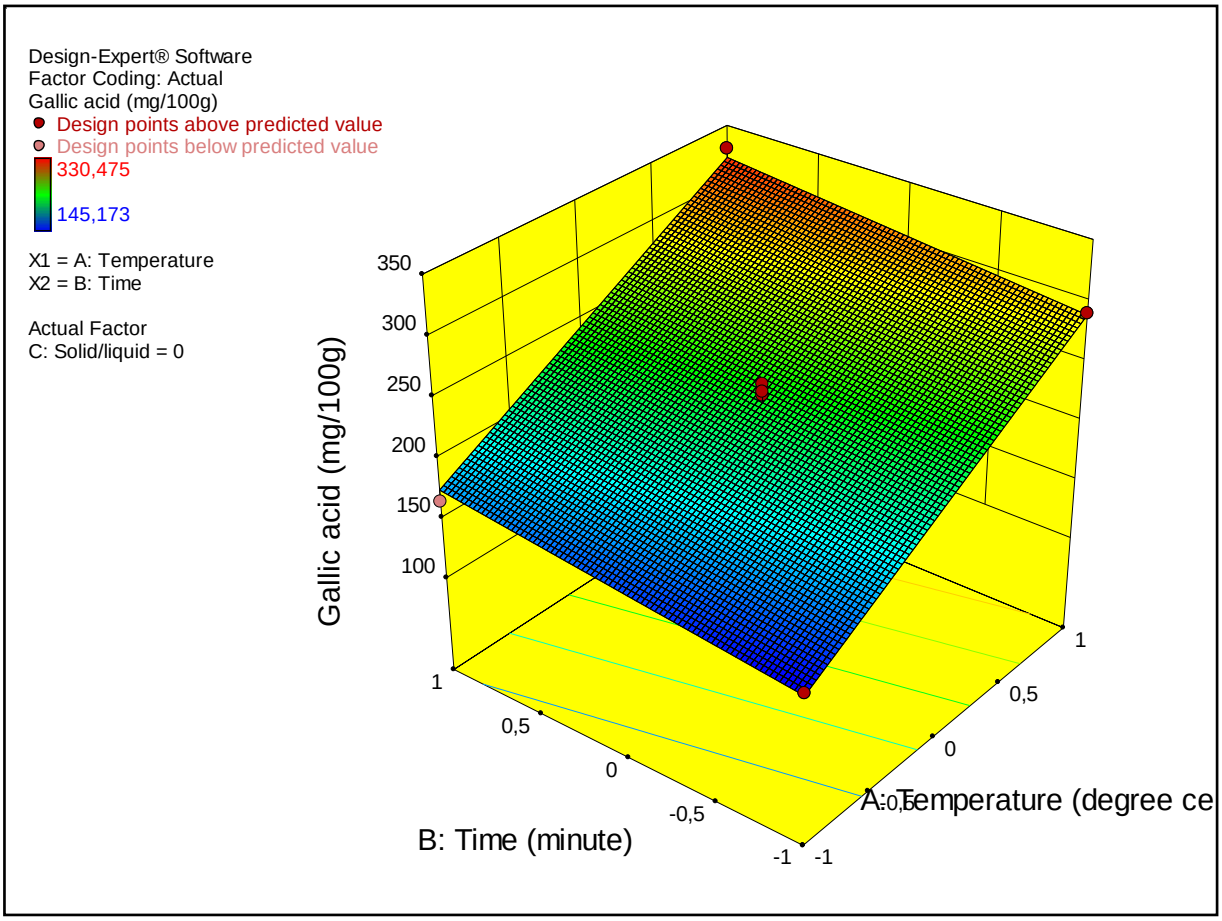

Figure 10. Three-dimensonal response surface of extraction yield depending on time and temperature.

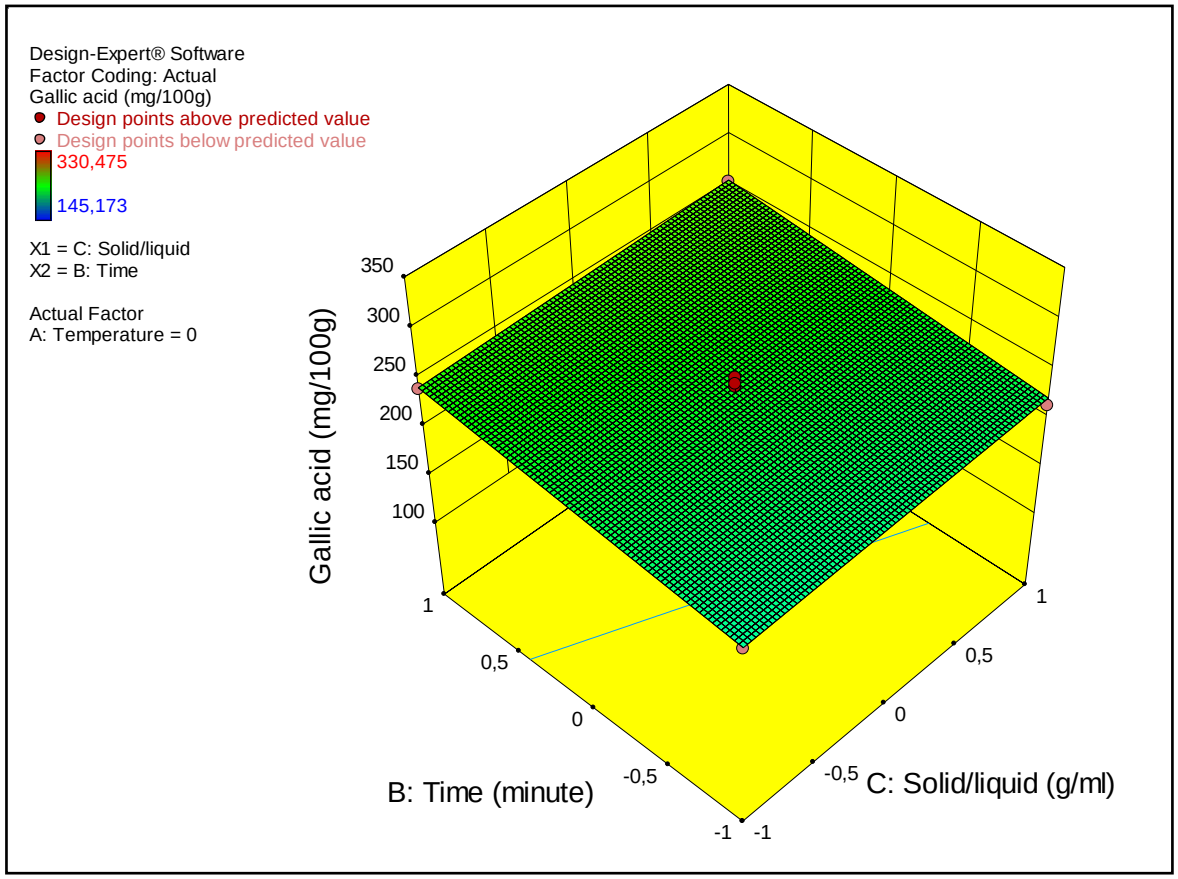

Figure 11. Three-dimensonal response surface of extraction yield depending on time and solid/liquid ratio.

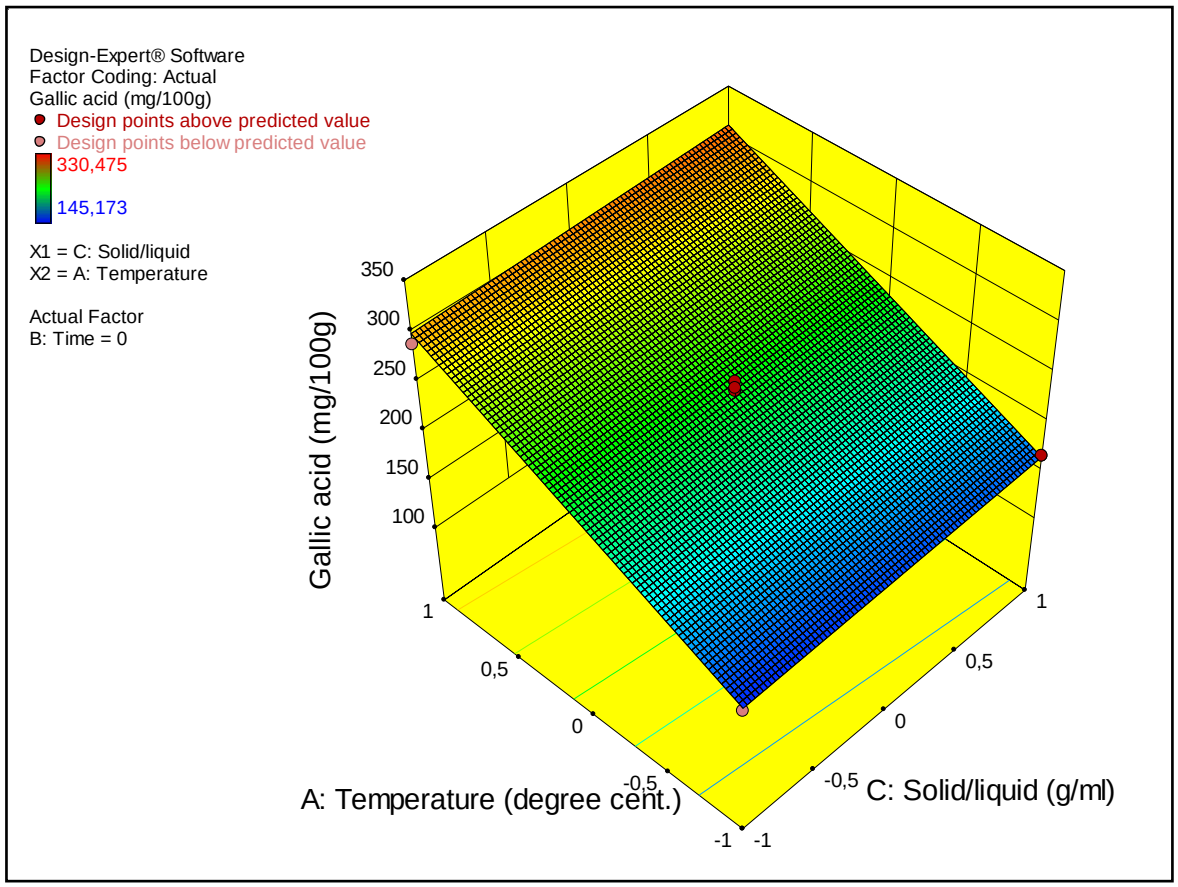

Figure 12. Three-dimensonal response surface of extraction yield depending on temperature and solid/liquid ratio.

As a result, the emprical relation explaining the response surface was found as:

$$\text{Gallic acid (mg/100g)} = +232.96487 + (73.42587).\text{temperature} + (16.48363).\text{time} + (6.37150).(^{\text{solid}}/_{\text{liquid}}) \quad (13)$$

Finally, the required extraction conditions were analyzed by using this equation and numerical analysis section of the software. In the analysis, restrictions of the parameters were selected as "in range" (has a meaning that they are in the experimental range), and the response criterion was determined as "max". As a result of the multi-parameter optimization, the optimum conditions producing the highest yield (5.29 mg GAE/g) were determined as 70°C, 90 minutes, 1/50 g/mL.

CONCLUSION

This research investigated the extraction of gallic acid equivalents of total phenolics of red pepper. At the experimental conditions of the study, the yield and kinetics of solid-liquid extraction were influenced especially by temperature. The extracted total phenolics were in the range of 1.39-3.27 mg GAE/g. Mass transfer model found as the most suitable model for the extraction kinetics of phenolics from red pepper. Temperature increased the diffusion coefficients. The results of this work could contribute in the optimization of extraction of total phenolics from *Capsicum annium* and in the design of drug-delivery systems including them in where the same value of diffusion coefficient may be more "natural" to the human body cells.

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