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Production of Effervescent Tablets with Phenolic Content

Sergen Cetebozan[1], Sibel Yigitarslan[2]
[1,2](Chemical Engineering, Suleyman Demirel University, Turkey)

Abstract: Currently, the individual needs a high immune system in order to fight against increasing diseases and/or epidemics. Macro, micro and functional foods that should be taken in the daily diet may be insufficient owing to various reasons. Therefore, the importance of the use of food supplements and functional foods which are recommended by experts has been increasing in recent years. In this study, effervescent tablet prototypes that support the immune system of the individual, which different antioxidant source (turmeric, cinnamon and pomegranate peel) and sodium-caseinate combinations,were produced with the aid of the Box-Behnken experimental design.Also some of the properties including dissolution time, pH, total acidity, density and viscosity, andamounts of phenolics, dry matter, sugar were optimized by means of Design Expert program.As a result, it was concluded that the combinations of parametersstudied had a remarkable effect on the dissolution time and phenolic content, wheres they did not have significant effect on other properties.
Keywords: Design Expert, Effervescent tablet, Antioxidant

1. INTRODUCTION

The intense work pace in the lives of individuals and the fact that the nutritional content of the foods consumed is less than in the past, causes them not to have adequate and/or balanced nutrition. The nutrition that does not meet the daily required amounts of macro/micro components that are essential for the body weakens the immune system. It has been revealed by many scientists that this situation causes cancer, heart, kidney diseases and even obesity, which are the biggest problems of today [1,2,3]. This nutrition-immunity relationship, which is handled by health scientists and health organizations, is also supported by food engineers. As a result, the importance of the concepts of functional-food, supplementary food or -food supplement has been increasing since 1984. These bioactive components of plant and animal origin can be consumed in the daily diet as powder, tablets and capsules[4]. Effervescent tablets dissolve in a liquid environment by forming gas bubbles as a result of acid-base reaction. These tablets have advantages such as providing faster absorption than capsule or pill form, increasing fluid intake and being easier to consume as they do not cause swallowing difficulties. Today,some effervescent tabletswith bioactive ingredientsincluding Acto-vit(vitamin C, zinc and turmeric extract), Sambucus Nigra (vitamin C, zinc, pomegranate peel and elderberry extract), Supradyn (Vitamin C, A, B3, B2, B1, E, Folic acid and various minerals), Liftoff (Vitamin C, B6, B12, Thiamine, Riboflavin, Niacin, Biotin and Pantothenic acid) are available in the market [5,6,7].

Another material that is essential for human health is proteins. Milk proteins are a rich source of bioactive peptides [8]. In addition to these components, milk contains many valuable substances such as calcium, folic acid, B6 (pyridoxine) and B12 (cyanocobalamin) and conjugated linoleic acid [9]. Casein, which makes up about eighty percent of milk and has an isoelectric point of 4.6, contains amino acids with high biological value (e.g. isoleucine, leucine, lysine, phenylalanine, threonine, tryptophan and valine). Casein composed of essential amino acids that cannot be synthesized in the human body is an easily digestible protein source [10,11]. It has been proven in studies that casein-derived bioactive peptides have antithrombotic, antihypertensive, antioxidative, antimicrobial and immunomodulatory effects on the cardiovascular, nervous, gastrointestinal and immune systems of individuals [12-13]. Sodium caseinate, which is a product obtained by reacting wet and/or dry casein in milk with dilute alkali solutions, is used in increasing the protein content of packaged food products, in the preparation of diet products, in enriching breads in terms of protein and lysine, in sausages, etc., due to its high protein content and nutritional value. It is frequently preferred in keeping the components together and increasing the shelf life of the products [12,14].

Another reason affecting human health is free radicals that cause oxidative damage to the cell. Antioxidants, another subgroup of food supplements and functional foods, are defined as substances that neutralize molecules with free radicals or directly inhibit oxidation reactions[15,16]. The main components responsible for the antioxidant effect in plants are phenolics, phenolic acids, saponins, tannins, coumarins, alkaloids and terpenoids [17]. The antioxidant activities of herbal bioactive (phenolic) compounds are due to their redox properties. As a result, oxidative damage can be prevented, delayed and/or eliminated. Phenolics are compounds found in the seeds, leaves, fruits and flowers of most plants. Almost all herbal medicines contain various phenolic derivatives. It has also been proven as a result of studies that these components have anti-inflammatory, antibacterial, antiallergic and antiviral effects [18].

The aim of this study is to produce effervescent tablets containing the combination of phenolic and sodium-caseinate components that support the body functions and immune systems of children and adults and to determine some properties of the obtained prototypes.In this way, an easily available and consumable supplement will be created that will support the individual's daily normal diet, immune, nervous, digestive, hormonal, respiratory and circulatory systems. As a result, it is aimed to present a product containing bioactive peptides and antioxidants together with its characteristic features as an alternative to existing effervescent tablets.

2. MATERIAL AND METHOD

In this study, sodium caseinate was first produced to form effervescent tablets. At this stage, the pasteurized semi-skimmed milk used was purchased from a regional market, and the chemicals of analytical purity were purchased from Sigma-Aldrich.Pure acetic acid was slowly added to 500 ml of milk on the heater set to stir at 40^{o}C and 400rpm until the ambient pH was about 4.6 (approximately 1.3 ml). It was kept for 10 minutes to ensure realization of equilibrium conditions and phase separation.After precipitation of the formed casein, casein and whey were separated from each other as soon as possible so that the dissociated molecules would not recombine. Filtration was carried out with a cotton filter, applying pressing to minimize the water content. Sodium hydroxide (1M) was slowly added to the obtained wet casein until the pH was 6.7-7.0 (1.7-2.2% by weight of casein solids) and sodium caseinate was obtained.Turmeric, cinnamon and pomegranate fruit peel obtained from herbalists were used to provide antioxidant effect of the final product, namely the effervescent tablet. The antioxidant-derived materials used were previously studied within our project team and were determined to have a high antioxidant content and/or diversity. [19,20,21,22,23]. Extraction was realized in an classical water bath (Memmert&GmbH+Co.KG)) in which temperature(50^{o}C), solid/liquid ratio (4g /160 ml) and time (90dakika) parameters investigated. After filtration, the extracts were mixed with the obtained sodium-caseinate at a rate of 30 g/90 ml and dried in a tray dryer (1500W) at 50^{o}C for 24 hours. The dried sodium caseinate-phenolic mixture was ground into powder.

Table 1.Parameters of Box-Behnken Experimental Design

Components	**-1**	**0**	**+1**
A: Lemon salt(mg)	240.0	365.0	450.0
A: Carbonate(mg)	540.5	822.0	1103.5
A: Phenolic – Sodium caseinate(mg)	460.3	700.0	939.7
B: D-glucose(mg)	250.0	400.0	550.0
C: Gelatine(mg)	150.0	200.0	250.0

In order to optimize the amounts of the components of the effervescent tablets, a separate Box-Behnken experiment design was used for each herbal source with the parameters given in Table 1. A, B, C parameters were mixed homogeneously in the specified amounts and then pressing was applied by keeping the cylinder in a stainless steel mold at 50^{o}C for 20 minutes.The formed effervescent tablets were dissolved in250 water and dissolution time, phenolic content, pH, total acidity, viscosity, density, soluble dry matter and reducing sugar content were analyzed. Nelson-Somogyi method was used for reducing sugar analysis and Folin-Ciocalteu method was used for total phenolic compounds [24,25].The data obtained as a result of the analyzes were investigated statistically with the help of the Design Expert program and the effect of the parameters on the effervescent tablet production was determined. In order to compare the results obtained, effervescent tablets from two different companies were obtained from the pharmacy (Herbalife Liftoff and Bayer Supradyn). These tablets were dissolved in 250 ml of water and the average dissolution time (110s), pH (4.30), viscosity (9.96 x 10-4 cP), density (0.994 g/cm3), dry matter (1.60), sugar (500,874 mg/ 100ml) and phenolic content (3710.565µg/100ml) of them were analyzed.

3. RESULTS

For the stated purpose, the turmeric (TEF), cinnamon (CEF) and pomegranate peel (PSET) effervescent tablets produced with the Box-Behnken experimental design were dissolved in 250 ml of water at room conditions and the above-mentioned analyzes were performed. The effects of A, B and C parameters on these results were determined with the same computer program and the optimum values of the parameters were determined.

Dissolution time of TET

According to the Design Expert program, for the predicted model to be valid, the model must be significant, if it has a lack of fit value, it must be not significant. Also, the value with the highest F value and the lowest P value gives the most effective parameter. When ANOVA table for dissolution time of TET was examined (Table 2), the Reduced Cubic Model recommended by the program was chosen since these requirements were met. The parameters coded as A, B and C represent the Lemon salt, carbonate and phenolic mixture, D-glucose, and gelatin amounts, respectively. The fact that the P value of the A parameter is less than 0.01 indicates that it has a significant effect on the result, while the B and C parameters do not have a significant effect on the dissolution time.The facts including fitness of the experimental and estimated values given in Figure 1 as do not create a deviation on the 45-degree line, high R^2 value (0.9996), low standart deviation (4.51) proves the compatibility of the model with the experimental data. The equation containing coded factors expressing the statistically validated model of the program was given in equation1.

Table2. Anova for Dissolution Time of TET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	93636.25	12	7803.02	383.64	0.0026	significant
A-A	*22473.01*	*1*	*22473.01*	*1104.90*	*0.0009*	
B-B	*369.99*	*1*	*369.99*	*18.19*	*0.0508*	
C-C	*319.16*	*1*	*319.16*	*15.69*	*0.0582*	
AB	*16150.60*	*1*	*16150.60*	*794.05*	*0.0013*	
AC	*4.49*	*1*	*4.49*	*0.22*	*0.6846*	
BC	*567.15*	*1*	*567.15*	*27.88*	*0.0340*	
A^2	*14570.76*	*1*	*14570.76*	*716.38*	*0.0014*	
B^2	*329.50*	*1*	*329.50*	*16.20*	*0.0565*	
C^2	*22.18*	*1*	*22.18*	*1.09*	*0.4060*	
A^2B	*6571.16*	*1*	*6571.16*	*323.08*	*0.0031*	
A^2C	*17.67*	*1*	*17.67*	*0.87*	*0.4497*	
AB^2	*15.76*	*1*	*15.76*	*0.78*	*0.4715*	
Pure Error	40.68	2	20.34			
Cor Total	93676.93	14				

Std.Dev.: 4.51 ; C.V.%: 6.19; R-Squared: 0.9996; Adj R-Squared: 0.9970; Pred R-Squared: N/A

$$Dissolution\ Time = +35.66 + 74.96A - 9.62B - 8.93C - 63.54AB - 1.06AC + 11.91BC + 62.82A^2 + 9.45B^2 - 2.45C^2 - 57.32A^2B + 2.97A^2C - 2.81AB^2 \quad (1)$$

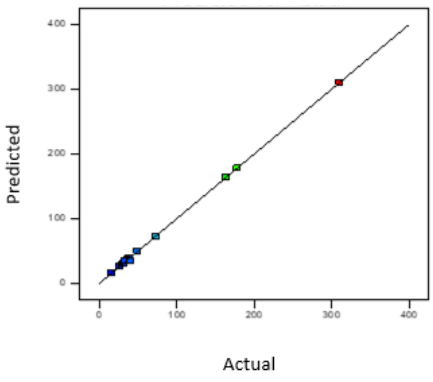


Figure1.Predicted and actual values for dissolution time of TET

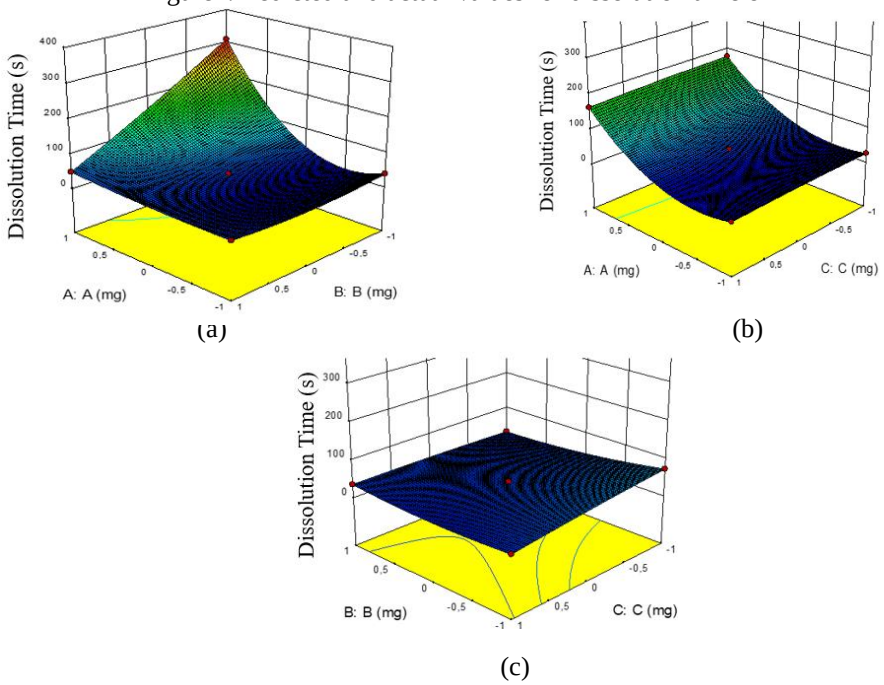


Figure2. Three-dimensional surfaces of dissolution time for the TET (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters.

The three-dimensional surface plots in Figure 2 include the dual effects of A, B, and C parameters on TET dissolution time. In Figure 2 (a), it can be seen that if parameter A was +1 and parameter B was -1, dissolution will take place at a maximum of 300 seconds. Since it was determined that the reference effervescent tablets were dissolved in water in an average of 110 seconds, it was determined that the desired dissolution time would be achieved if the A and B parameters were set to 0. As demonstrated in Figure (b), taking the A parameter in the +0.5 to +1 value range and the C parameter in the -1 and +1 value range would allow the effervescent tablet to dissolve in 50% less time than dual effect of AB.In graph (c), it is seen that the dual effect of B and C has no effect on the resolution time. In order to achieve dissolution in the same time as the reference effervescent tablets, it was deduced that the optimum values of A, B and C parameters should be +1.000, +0.500 and -0.285, respectively.

Phenolic content of TET

The fact that the R^2 value very close to 1 and the CV value of 0.66% is in an acceptable range shows the suitability of the reduced qubic model for the optimization of the values obtained from the TET phenolic analysis (Table 3). According to the ANOVA, the single effects of parameters A, B and C on the result were found to be 98.12%, 1.35% and 0.53%, respectively. A P value of 0.0002 of parameter A showed a significant effect, while respective values of B and C greater than 0.01 showed no significant effect. The parameter A, which has the most effective one, was an expected result since one of the components in it was a phenolic source. The fact that all of the experimental and estimated values are on the 45-degree line in Figure 3 supports the compatibility of the selected model with the experimental data and that there is no significant standard deviation. The equation expressing the TET phenolic content in terms of the coded factors is included in equation 2.

Table3. Anova for phenolic content of TET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	1.660×10^6	12	1.384×10^5	1226.67	0.0008	significant
A-A	*7.376×10^5*	*1*	*7.376×10^5*	*6539.53*	*0.0002*	
B-B	*10127.40*	*1*	*10127.40*	*89.78*	*0.0110*	

C-C	*3994.87*	*1*	*3994.87*	*35.42*	*0.0271*
AB	*1.220* x 10^5	*1*	*1.220* x 10^5	*1081.40*	*0.0009*
AC	*7586.41*	*1*	*7586.41*	*67.26*	*0.0145*
BC	*3994.87*	*1*	*3994.87*	*35.42*	*0.0271*
A^2	*1807.44*	*1*	*1807.44*	*16.02*	*0.0571*
B^2	*3324.74*	*1*	*3324.74*	*29.48*	*0.0323*
C^2	*3.252* x 10^5	*1*	*3.252* x 10^5	*2883.26*	*0.0003*
A^2B	*1.615* x 10^5	*1*	*1.615* x 10^5	*1431.37*	*0.0007*
A^2C	*2113.48*	*1*	*2113.48*	*18.74*	*0.0494*
AB^2	*81646.38*	*1*	*81646.38*	*723.83*	*0.0014*
Pure Error	225.59	2	112.80		
Cor Total	1.661 x 10^6	14			

Std. Dev.: 10.62; C.V.: %0.66; R-Squared: 0.9999; ADJ R-Squared: 0.9990; Pred. R-Squared: N/A

$$\textit{Amount of phenolic} = +1449.48 + 429.43A + 50.32B - 31.60C - 174.63AB - 43.55AC + 31.60BC - 22.12A^2 + 30.01B^2 + 296.78C^2 - 284.13A^2B - 32.51A^2C - 202.05AB^2 \quad (2)$$

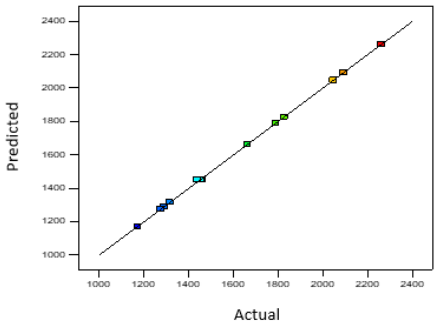
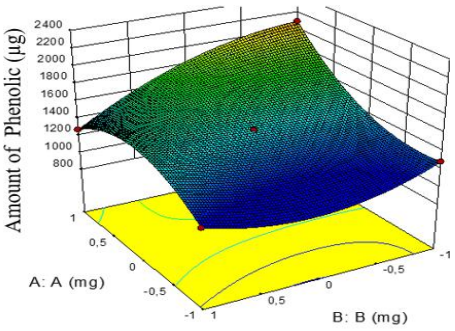
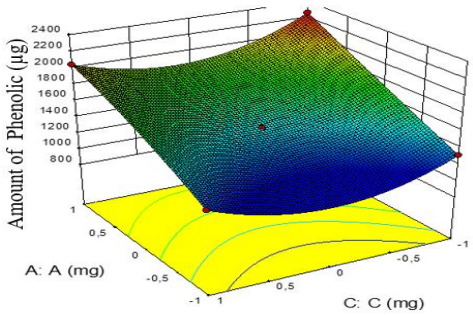


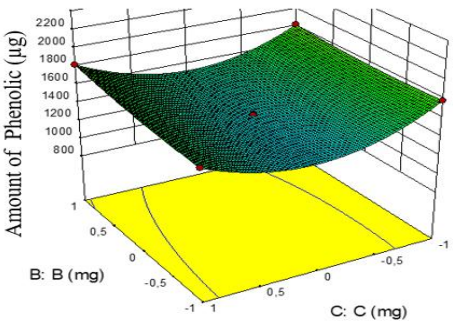
Figure3. Predicted and actual values for phenolic content of TET



(a)



(b)



(c)

Figure 4. Three-dimensional surfaces of phenolics for the TET (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters

Figure 4.(a) shows that the phenolic content in the tablet will be at its maximum value (2500 µg) if the parameter A is taken as +1 and B as -1. It was determined that taking parameter A at the maximum value and parameter B at 0 value will cause a 14.3% decrease by mass in the total phenolic content. In Figure 4.(b), it has been determined that taking parameter A as +1 and parameter C as -1 will increase the phenolic content in the tablet to the maximum value (2200 µg). It was determined that changing the C parameter between +1 and -1 values while the A parameter was constant at +1 did not significantly change the amount of phenolic in the tablet (1900 µg), and only caused a change of 18% by mass. In Figure 4.(c), it is seen that the dual effects of B and C parameters do not play a decisive role on the total phenolic content. As a result, it was determined that the maximum content of phenolic compounds (2471.568 µg) in the tablet was determined in the production conditions carried out at A(+0.985), B(-0.826) and C(-0.970).

Dissolution time of CET

The single and dual effects of A, B and C parameters on CET dissolution time were given in Table 4. Since the R^2 value was 1 and its standard deviation was within the acceptable range, it was decided that the proposed reduced qubic model would be suitable. The individual parameters affecting the dissolution time were C, A, and B, respectively. Since all of the P values are less than 0.01, all parameters have a significant effect on the result. When the dual effects were examined, it was decided that the orderof them was AB, BC and AC, respectively. The fact that the experimental and estimated values are on the same line (Figure 5.) statistically supported the accuracy of the model. The equation expressing the surface was given in equation 3.

Table4. Anova for Dissolution Time of CET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	2.952×10^6	12	2.460×10^5	11345.78	< 0.0001	significant
A-A	*1.890×10^5*	*1*	*1.890×10^5*	*8714.49*	*0.0001*	
B-B	*2804.23*	*1*	*2804.23*	*129.33*	*0.0076*	
C-C	*2.469×10^5*	*1*	*2.469×10^5*	*11387.07*	*< 0.0001*	
AB	*94710.06*	*1*	*94710.06*	*4367.96*	*0.0002*	
AC	*1357.19*	*1*	*1357.19*	*62.59*	*0.0156*	
BC	*26242.38*	*1*	*26242.38*	*1210.28*	*0.0008*	
A^2	*1.391×10^6*	*1*	*1.391×10^6*	*64171.50*	*< 0.0001*	
B^2	*7.752×10^5*	*1*	*7.752×10^5*	*35749.45*	*< 0.0001*	
C^2	*3.393×10^5*	*1*	*3.393×10^5*	*15649.20*	*< 0.0001*	
A^2B	*95639.70*	*1*	*95639.70*	*4410.84*	*0.0002*	
A^2C	*1.275×10^5*	*1*	*1.275×10^5*	*5880.67*	*0.0002*	
AB^2	*32072.85*	*1*	*32072.85*	*1479.18*	*0.0007*	
Pure Error	43.37	2	21.68			
Cor Total	2.952×10^6	14				

(Std. Dev.: 4.66; C.V. %: 0.69; R-Squared: 1.0000; Adj R-Squared: 0.9999; Pred R-Squared:N/A)

$$\begin{aligned} Dissolution\ Time &= +1412.67 - 217.35A \\ &+ 26.48B + 248.45C \\ &+ 153.88AB + 18.42AC \\ &- 81.00BC - 613.88A^2 \\ &- 458.19B^2 - 303.15C^2 \\ &- 218.68A^2B \\ &+ 126.63AB^2 \quad (3) \end{aligned}$$

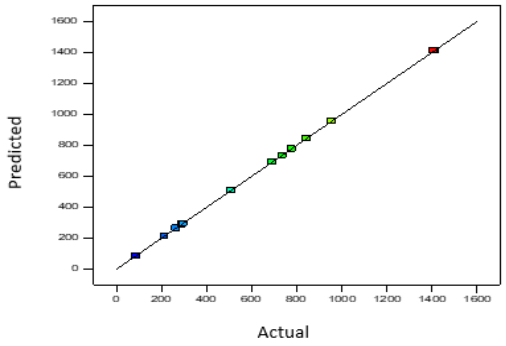


Figure5. Predicted and actual values for Dissolution time of CET.

The three-dimensional surface plots in Figure 6 (a), (b) and (c) show the dual effects of parameters A, B, and C affecting the CET dissolution time. In Figure 6(a), the values of A and B parameters being 0 indicated that the dissolution time would take place in a maximum of 700 seconds. Taking parameter B between +0.5 and -0.5 and parameter C between +1 and +0.5 caused an 85.71% increase in dissolution time (Figure 6.(b)). The same increase in time was also seen in the dual effect of AC parameters in Figure 6(c). As the C parameter for CET gets closer to the value of +1, it had been determined that it caused a significant increase in the dissolution time. Considering the dissolution time of the reference tablets, it was concluded that parameter C (amount of gelatin) should be close to the value of -1. In order for the effervescent tablet to dissolve in the desired time and the phenolic value to be maximum, it was decided that the optimum values of the parameters A, B and C were (+1.000, -0.992 and -0.637), respectively.

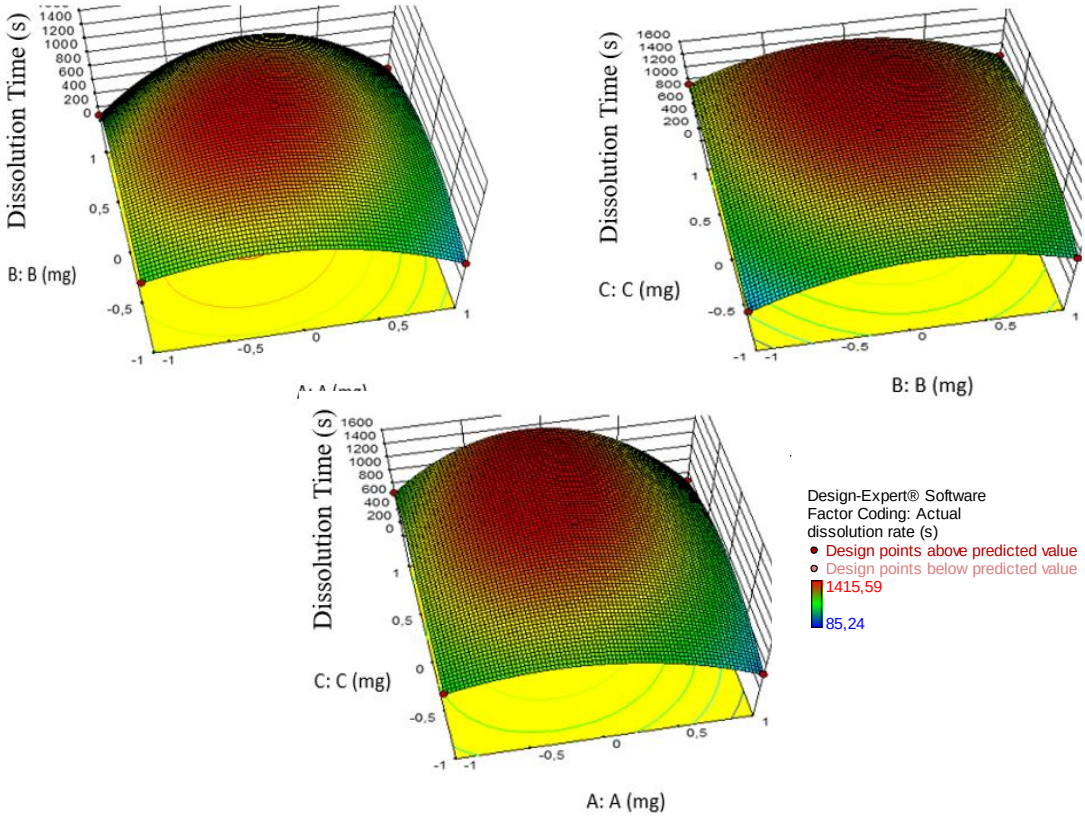


Figure 6. Three-dimensional surfaces of dissolution time for the CET (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters.

Phenolic content of CET

Similarly, the acceptable values of R^2 (0.9994), standard deviation (72.34) and coefficient of variance (2.29%) in Table 5 showed the suitability of the reduced qubic model. F value of parameter A was the highest and thus it was the most effective parameter (74.05%) due to the fact that it contains cinnamon-derived phenolics itself. The phenolic content s affected by the parameter C by 24.06% and the parameter B by 1.89%. The placement of the results on the 45-degree line (Figure 7.) proved the compatibility of the model, and the equation expressing the surface was represented in equation 4.

Table5. Anova for Phenolic content of CET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1.782×10^7	12	1.485×10^6	283.84	0.0035	significant
A-A	*5.400* x 10^6	*1*	*5.400* x 10^6	*1031.93*	*0.0010*	
B-B	*1.379* x 10^5	*1*	*1.379* x 10^5	*26.36*	*0.0359*	
C-C	*1.754* x 10^6	*1*	*1.754* x 10^6	*335.21*	*0.0030*	
AB	*1.907* x 10^5	*1*	*1.907* x 10^5	*36.44*	*0.0264*	
AC	*2.004* x 10^6	*1*	*2.004* x 10^6	*383.06*	*0.0026*	
BC	*2.632* x 10^5	*1*	*2.632* x 10^5	*50.30*	*0.0193*	
A^2	*5.144* x 10^5	*1*	*5.144* x 10^5	*98.31*	*0.0100*	
B^2	*48639.00*	*1*	*48639.00*	*9.30*	*0.0928*	
C^2	*8.456* x 10^5	*1*	*8.456* x 10^5	*161.60*	*0.0061*	
A^2B	*6229.40*	*1*	*6229.40*	*1.19*	*0.3892*	
A^2C	*4.803* x 10^6	*1*	*4.803* x 10^6	*917.78*	*0.0011*	
AB^2	*1.485* x 10^5	*1*	*1.485* x 10^5	*28.39*	*0.0335*	
Pure Error	10465.59	2	5232.79			
Cor Total	1.783×10^7	14				

(Std. Dev.:72.34; C.V. %: 2.29; R-Squared:0.9994; Adj R-Squared: 0.9959; Pred R-Squared: N/A)

$$Amount\ of\ phenolic = +3161.01 + 1161.88A - 185.71B - 662.21C + 218.34AB + 707.90AC + 256.53BC - 373.26A^2 - 114.77B^2 + 478.57C^2 - 55.81A^2B + 1549.61A^2C - 272.52AB^2 \quad (4)$$

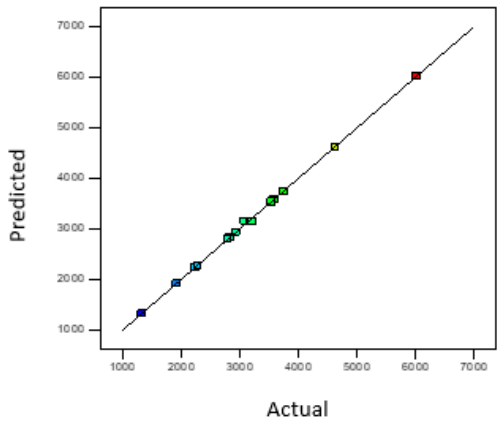
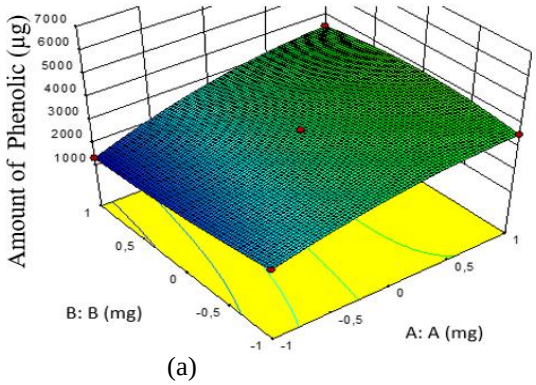
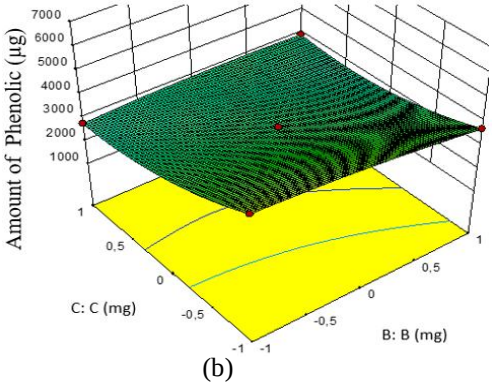


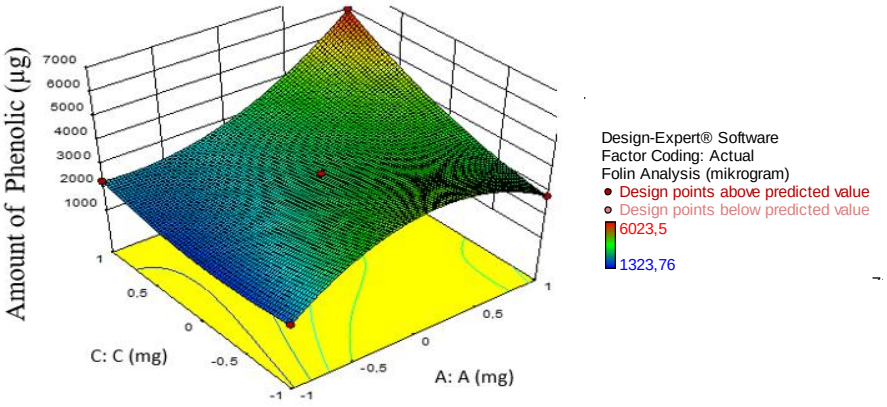
Figure7. Predicted and actual values for phenolic content of CET



(a)



(b)



(c)

Figure8. Three-dimensional surfaces of phenolics for the Cinnamon Effervescent tablet (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters.

In Figure 8(a), it can be seen that if the A parameter was in the range of +0.5 to +1 and the B value was 0, then the amount of phenolic in the tablet would be approximately 4000 µg. A 1-unit change in parameter A reduced the phenolic content by 50%. In Figure 8(b), it was determined that the maximum value of the BC binary parameters reduced the phenolic content by approximately 700 µg. It is seen on the surface in Figure 8(c) that taking the A and B parameters as +1 will produce a maximum of approximately 6000 µg of phenolic substance and was the most effective binary parameter. As a result, the conditions for producing tablets containing a maximum of 6049.2 µg phenolic substance were optimized as A(+1.000), B(+0.189) and C(0.999).

Dissolution time of PSET

The single and dual effects of A, B and C parameters affecting PSET dissolution time were given in Table 6. Since the R^2 value was 0.9994, Adj-R2 was 0.9956 and its standard deviation was in the acceptable range, the proposed reduced qubic model was applied. When the F values were examined, the individual parameters affecting the dissolution time were A, B and C, respectively. A parameter affected 71.96%. Considering the P values, it was concluded that each of the A and B parameters alone had a real effect on the dissolution time, while the C parameter did not have a significant effect. When the dual effects were examined, it was decided that the order was AB, BC and AC. In Figure 9, the suitability of the model has been proved statistically. The equation representing the optimized surface in terms of coded factors was given in equation 5.

Table6. Anova for Dissolution Time of PSET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	6.269 x 10^5	12	52245.31	266.56	0.0037	significant
A-A	*1.923* x 10^5	*1*	*1.923* x 10^5	*981.03*	*0.0010*	
B-B	*72900.00*	*1*	*72900.00*	*371.94*	*0.0027*	
C-C	*2025.00*	*1*	*2025.00*	*10.33*	*0.0847*	
AB	*4692.25*	*1*	*4692.25*	*23.94*	*0.0393*	
AC	*380.25*	*1*	*380.25*	*1.94*	*0.2983*	
BC	*900.00*	*1*	*900.00*	*4.59*	*0.1654*	
A^2	*1.767* x 10^5	*1*	*1.767* x 10^5	*901.44*	*0.0011*	
B^2	*5331.69*	*1*	*5331.69*	*27.20*	*0.0349*	
C^2	*84746.77*	*1*	*84746.77*	*432.38*	*0.0023*	
A^2B	*81003.13*	*1*	*81003.13*	*413.28*	*0.0024*	
A^2C	*5995.13*	*1*	*5995.13*	*30.59*	*0.0312*	
AB^2	*25088.00*	*1*	*25088.00*	*128.00*	*0.0077*	
Pure Error	392.00	2	196.00			

Cor Total 6.273 x 10^5 14

(Std. Dev.: 14.00; C.V. %:2.98; R-Squared: 0.9994; Adj R-Squared: 0.9956; Pred R-Squared:N/A)

$$Dissolution\ Time = +526.0 + 219.25A - 135.0B - 22.50C + 34.25AB + 9.75AC - 15.0BC - 218.75A^2 - 38.0B^2 + 151.50C^2 + 201.25A^2B + 54.75A^2C - 112.0AB^2 \quad (5)$$

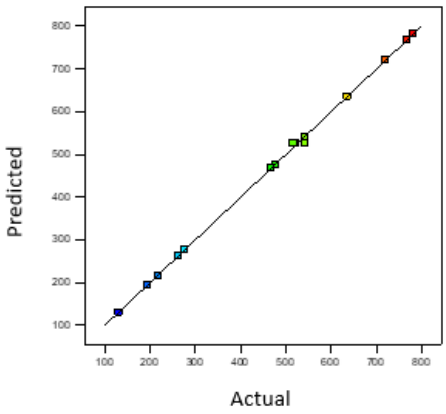
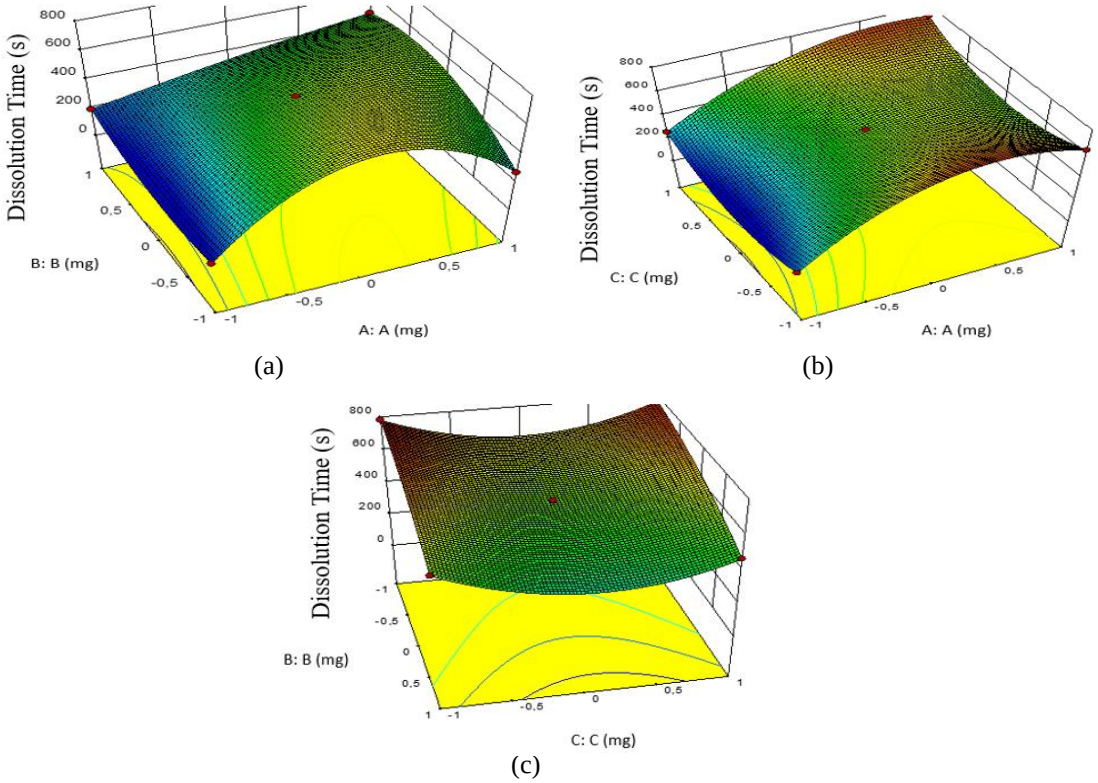


Figure9.Predicted and actual values for Dissolution time of PSET.



(a) (b)

(c)

Figure 10. Three-dimensional surfaces of dissolution time ofPSET (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters.

The three-dimensional surface graphs above show the dual effects of A, B, and C parameters affecting the dissolution time of PSET. Figure 10(a) shows that a value between -0.5 and -1 for parameter A and 0 to -1 for parameter B will reach the desired reference dissolution time of the effervescent tablet. A value of -1 for parameter A and a value between 0 and -0.5 for C provides the desired reference dissolution time (Figure 10(b)). In Figure 10(c), it is seen that having the parameter B at a value of -1 and C with a value of +1 or -1 causes the tablet to dissolve in 7.27 times longer. The optimum conditions of parameters A, B, and C for the desired reference resolution time were determined as -0.973, -0.196, and 0.288, respectively. The conditions for the

maximum phenolic content of the effervescent tablet are 1.000, -1.000 and -0.188, respectively. Under these conditions, the tablet dissolves in 270.64 seconds.

Phenolic content ofPSET

For the surface, which reveals the single and dual effects of A, B and C parameters on the phenolic content of the pomegranate-derived effervescent tablet, in line with the previously described criteria (R^2 = 0.9982, Adj. R^2 = 0.9875, Std. Dev. = 15.07, Coeff. Variance =5.18) the reduced qubic model was found to be suitable (Table 7). Since the highest F value and P value less than 0.01 (0.0042), parameter A was the most effective parameter (68.24%) to determine the phenolic content in the effervescent tablet. It was concluded that the second most effective parameter with a rate of 31.15% was the B parameter, and C did not have an effect on its own. As a result of the statistically verified model (Figure 11) the equation expressing the surface was given in equation 6.

Table7. Anova for phenolic content of PSET

ANOVA for Response Surface Reduced Cubic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	2.544 x 10^5	12	21199.47	93.28	0.0107	significant
A-A	*53393.58*	*1*	*53393.58*	*234.95*	*0.0042*	
B-B	*478.16*	*1*	*478.16*	*2.10*	*0.2840*	
C-C	*24378.37*	*1*	*24378.37*	*107.27*	*0.0092*	
AB	*3845.30*	*1*	*3845.30*	*16.92*	*0.0543*	
AC	*42545.79*	*1*	*42545.79*	*187.22*	*0.0053*	
BC	*758.76*	*1*	*758.76*	*3.34*	*0.2092*	
A^2	*35652.84*	*1*	*35652.84*	*156.88*	*0.0063*	
B^2	*20370.49*	*1*	*20370.49*	*89.64*	*0.0110*	
C^2	*16434.36*	*1*	*16434.36*	*72.32*	*0.0135*	
A^2B	*3302.11*	*1*	*3302.11*	*14.53*	*0.0624*	
A^2C	*466.60*	*1*	*466.60*	*2.05*	*0.2883*	
AB^2	*51358.86*	*1*	*51358.86*	*226.00*	*0.0044*	
Pure Error	454.51	2	227.25			
Cor Total	2.548 x 10^5	14				

(Std. Dev.: 15.07; C.V. %:5.18; R-Squared: 0.9982; Adj R-Squared: 0.9875; Pred R-Squared; N/A)

$$Amount\ of\ phenolic = +234.77 - 115.54A + 10.93B + 78.07C + 31.01AB - 103.13AC + 13.77BC + 98.26A^2 + 74.28B^2 - 66.72C^2 + 40.63A^2B + 15.27A^2C + 160.25AB^2 \quad (6)$$

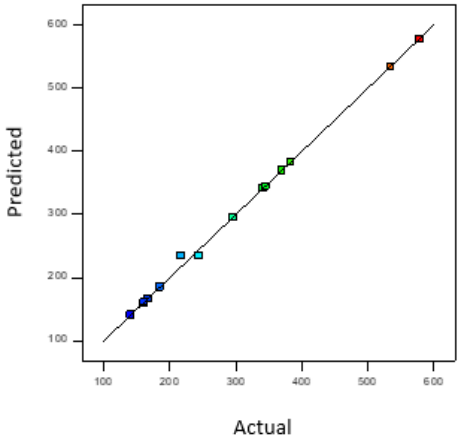
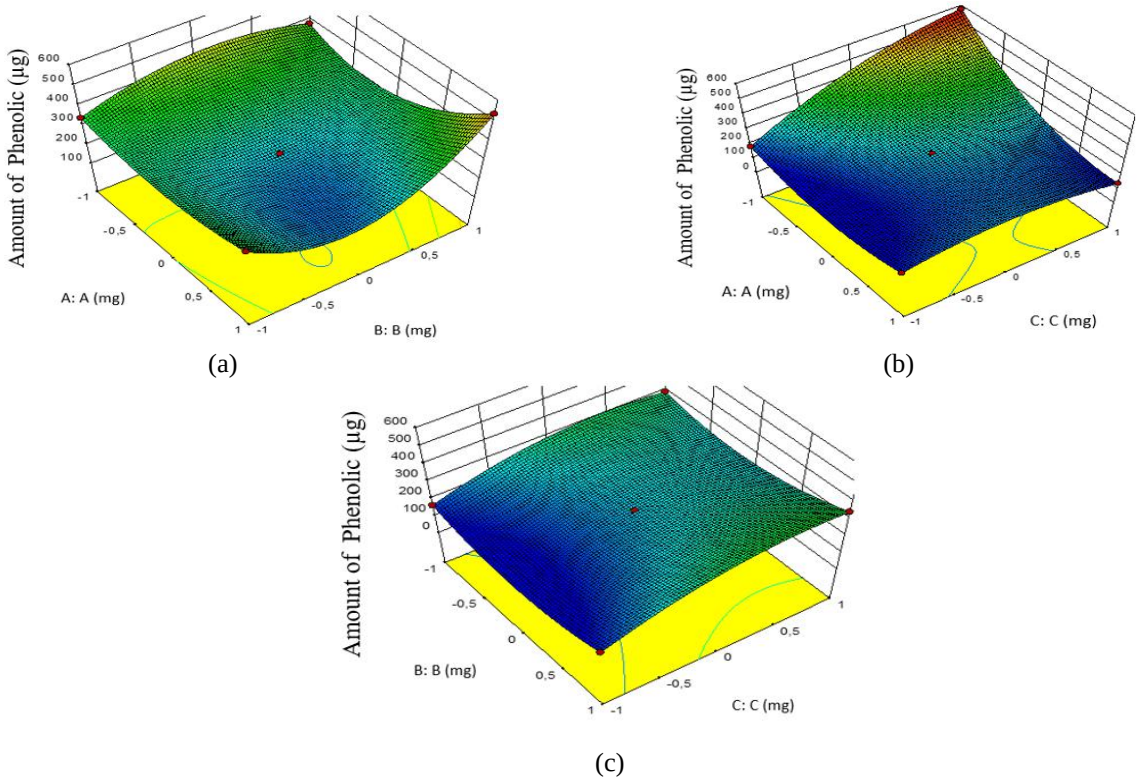


Figure11.Predicted and actual values for phenolic content of PSET

It had been determined that when the A and B parameters were at +1, the amount of phenolic in the tablet would be maximum (approximately 500 µg), and when the parameter A was -1 and B was 0, the amount of phenolic in the tablet will decrease by 1.25 times (Figure 12(a)). If A was -1 and C was +1, the AC dual effect provided the maximum phenolic content (600 µg) (Figure 12(b)). The dual effect of the BC parameters was 50% less than the AB dual effect (Figure 12(c)). In order to obtain the maximum amount of phenolic (580,660 µg), A, B and C parameters should take the values of -0.998, +0.206 and +0.994, respectively.



(a) (b)

(c)

Figure 12. Three-dimensional graphs of phenolic content of PSET (a) the dual effect of AB parameters, (b) the dual effect of AC parameters, (c) the dual effect of BC parameters.

Other characteristics of TET, CET and PSET

The analyzed characteristics (pH, dry matter, sugar, total acidity, viscosity and density) of all tablets produced under optimum conditions were given in Table 8. Generally, it was determined that the parameters examined with the Box-Behnken experimental design did not cause a significant change on the said properties of the effervescent tablets. The pH values of effervescent tablets containing turmeric, cinnamon and pomegranate extract were measured as 6.81, 7.00 and 7.00, respectively, when optimum conditions were met. In the dry matter analysis, the model equation of all three tablet types, the R^2 values were very close to 1.0 and the reduced qubic model was chosen because it did not contain any aliases. It was determined that the parameter that most affected the sugar content of all effervescent tablets was B; and when the F values were compared, it affected the result by 95% in TET, 93% in CET and 77% in PSET. Total acidity values were explained with reduced qubic model for PSET and CET, while TET was explained with linear one. The viscosity value expressed by the reduced qubic model was constant (0.001cP) in all effervescent tablets. The average density of TET, CET and PSET is 0.993g/cm^3. For TET, the fact that all viscosity values were the same in the Box-Behnken experimental design showed that A, B and C parameters have no effect on the result.

Table8. Other characteristics of TET, CET and PSET

Other characteristics ofTET					
pH					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Linear	0.5262	A=4.57 B=4.37 C=3.28	A=0.0559 B=0.0606 C=0.0974	Significant	6.809 A=1.000 B=0.580 C=-0.071
Cubic	0.9460			not-significant	
Quadratic	0.7227			not-significant	
Dry Matter					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduce Cubic	0.9919	A=3.95 B=3.95 C=3.95	A=0.1853 B=0.1853 C=0.1853	Significant	0.203 A=1.000 B=-0.612 C=-0.635
Cubic	0.9919			Aliased	
Quadratic	0.8314			not-significant	
Sugar					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Quadratic	0.9426	A=1.11 B=54.28 C=1.56	A=0.3410 B=0.0007 C=0.2666	Significant	1016.987 A=1.000 B=-0.960 C=-0.596
Qubic	0.9931			Aliased	
Linear	0.6541			Significant	
Total Acid					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Linear	0.4961	A=9.54 B=0.54 C=0.75	A=0.0103 B=0.4798 C=0.4036	Significant	0.901 A=1.000 B=-0.398 C=0.901
Quadratic	0.6892			not-significant	
Qubic	0.8494			not-significant	
Viscosity					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduce Cubic	0.9990	A=137.29 B=32.14 C=51.57	A=0.0072 B=0.0297 C=0.0188	Significant	0.001 A=1.000 B=-0.577 C=-0.856
Qubic	0.9990			Aliased	
Quadratic	0.9080			Significant(Lack of Fit)	
Density					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Mean	0.0000	A= - B= - C= -	A= - B= - C= -		0.992 A=1.000 B=0.000 C=-1.000
Linear	0.1154			not-significant	

Qubic	0.9771			not-significant	
Other characteristics of CET					
pH					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9975	A=10.71 B=27.43 C=10.71	A=0.0820 B=0.0346 C=0.0820	Significant	7.000 A=1.000 B=0.821
Cubic	0.9975			Aliased	C=-0.829
Quadratic	0.7222			Not Significant	
Dry Matter					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9932	A=60.75 B=27.00 C=0.000	A=0.0161 B=0.0351 C=0.000	Significant	0.474 A=1.000 B=-0.740
Cubic	0.9932			Aliased	C=0.957
Quadratic	0.8269			Not Significant	
Sugar					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9951	A=3.12 B=155.53 C=8.11	A=0.2192 B=0.0064 C=0.1044	Significant	770.359 A=1.000 B=-0.154
Cubic	0.9951			Aliased	C=-0.199
Quadratic	0.7587			Not Significant	
Total Acid					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9948	A=157.69 B=0.19 C=9.19	A=0.0063 B=0.7072 C=0.0938	Significant	0.300 A=1.000 B=1.000
Cubic	0.9948			Aliased	C=0.000
Quadratic	0.9585			Significant	
Viscosity					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9998	A=4.00 B=342.25 C=999.25	A=0.1835 B=0.0029 C=0.0010	Significant	0.001 A=1.000 B=-0.474
Cubic	0.9998			Aliased	C=-0.550
Quadratic	0.7283			Not Significant	
Density					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9993	A=12.25 B=441.00 C=25.0	A=0.0728 B=0.0025 C=0.0377	Significant	0.996 A=1.000 B=0.552
Cubic	0.9993			Aliased	C=-0.621
Quadratic	0.6940			Not Significant	

Other characteristics of PSET					
pH					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9981	A=240.25 B=9.00 C=100.00	A=0.0041 B=0.0955 C=0.0099	Significant	7.001 A=1.000 B=0.898
Cubic	0.9981			Aliased	C=-0.845
Quadratic	0.8976			Significant	
Dry Matter					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9949	A=126,75 B=3,00 C=12,00	A=0.0078 B=0.2254 C=0.0742	Significant	0.507 A=1.000 B=0.685
Cubic	0.9949			Aliased	C=-0.879
Quadratic	0.5603			Not Significant	
Sugar					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9955	A=8.095 x10^{-5} B=192.25 C=56.35	A=0.9365 B=0.0052 C=0.0173	Significant	200.779 A=1.000 B=-0.122
Cubic	0.9955			Aliased	C=0.847
Quadratic	0.7004			Not Significant	
Total Acid					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9976	A=379.31 B=11.81 C=0.67	A=0.0026 B=0.0752 C=0.4992	Significant	1.004 A=1.000 B=-0.491
Cubic	0.9976			Aliased	C=-0.794
Quadratic	0.9840			Significant	
Viscosity					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9991	A=1008.00 B=112.00 C=20.57	A=0.0010 B=0.0088 C=0.0453	Significant	0.001 A=1.000 B=0.000
Cubic	0.9991			Aliased	C=-1.000
Quadratic	0.7790			Not-Significant	
Density					
		Parameters			**Predicted value and optimum conditions**
Model	**R-Squared**	**F value**	**P value**		
Reduced Cubic	0.9980	A=24.67 B=12.79 C=83.53	A=0.0382 B=0.0701 C=0.0118	Significant	0.990 A=1.000 B=0.768
Cubic	0.9980			Aliased	C=-0.458
Quadratic	0.5724			Not-Significant	

4. CONCLUSION

In this study, the production and optimization of some properties of effervescent tablet prototypes containing different antioxidant-and-bioactive peptide sources named sodium-caseinate, which support the immune mechanism of individuals, were carried out. It was observed that the A, B and C parameters examined with the Box-Behnken experimental design had significant effect on the dissolution time and phenolic content, and did not have any effect on the pH, total acidity, viscosity, density, and amounts of dry matter and sugar of tablets. While the effect of parameter C on dissolution time was highest for CET, A was the most effective parameter for TET and PSET. This is because combining cinnamon extract with sodium-caseinate in the experimental phase creates stickier structure than other tablets, and therefore functions similarly to gelatin (as parameter C). It was observed that PSET contained the maximum amount of phenolic and dissolved in 2.5 times longer than the dissolution time of reference effervescent tablets.In line with the purpose of the study, it has been demonstrated that effervescent tablets providing the maximum amount of phenolic that one needs to take daily can be produced. It has been concluded that the dissolution time of these tablets is longer than the existing (reference) effervescent tablets, which is not a limiting factor since the type and amount of phenolics are important criteria to support health. With this study, it has been proven that a new product can be developed in the form of effervescent tablets, which has a positive effect on the immune system of the individual in the field of functional food and supplementary food.

5. Acknowledgements

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