ISSN: 2347-467X, Vol. 09, No. (3) 2021, Pg. 745-754

Current Research in Nutrition and Food Science

www.foodandnutritionjournal.org

An Overview on the Use of Response Surface Methodology to Model and Optimize Extraction Processes in the Food Industry

VICENTE AMIRPASHA TIRADO-KULIEVA[1], MANUEL SÁNCHEZ-CHERO[1]*, MARIO VILLEGASYARLEQUÉ[2], GRETELL FIORELA VILLEGAS AGUILAR[3], GILBERTO CARRIÓN-BARCO[4], ABRAHAM GUILLERMO YGNACIO SANTA CRUZ[5] and JOSÉ SÁNCHEZ-CHERO[2]

[1]Facultad de Ingeniería de Industrias Alimentarias, Universidad Nacional de Frontera, Sullana, Perú.
[2]Facultadde Ingeniería Económica, Universidad Nacional de Frontera, Sullana, Perú.
[3]Facultad de Negocios, Universidad Privada del Norte, Trujillo, Perú.
[4]Carrera de Ingeniería de Sistemas e Informática, Universidad Tecnológica del Perú, Chiclayo, Perú.
[5]Escuela Profesional de Ingeniería de Industrias Alimentarias, Universidad Nacional Pedro Ruíz Gallo, Lambayeque, Perú.

Abstract

Response surface methodology (RSM) is a widely used tool for modeling and optimization for food processes. The objective of this review is to evaluate recent findings on the use of RSM in the extraction of compounds from agri-food products. First, the steps for the application of RSM were briefly detailed. According to the analysis performed, RSM is suitable because it evaluates the effects of the independent variables and their interactions on the responses, which is ideal for the optimization of different techniques for the extraction of multiple bioactive compounds and therefore, in the various studies, has allowed to significantly increase the yield and even the biological activities of the extracts; however, RSM has limitations and considering the complexity and dynamics of foods, the challenge is much greater. In this sense, it was determined that simultaneous use with other techniques is necessary in order to optimally describe the process and obtain more accurate results.

Article History
Received: 26 May 2021
Accepted: 24 August 2021

Keywords
Agri-Food;
Bioactive Compounds;
Design;
Modeling;
Optimization;
Rsm;
Variables.

Introduction

Currently, in all industries the optimization of processes is essential to establish the best operating parameters, obtaining better results and at the same time, saving costs and production time. For this, it is necessary to apply mathematical and statistical

CONTACT Manuel Sánchez-Chero msanchezch@unf.edu.pe Facultad de Ingeniería de Industrias Alimentarias, Universidad Nacional de Frontera, Sullana, Perú.

Doi: http://dx.doi.org/10.12944/CRNFSJ.9.3.03

methods with scientific validity[1, 2] that help predict the behavior of the variables of interest.[3] Before the 1950s, techniques were used that only analyzed one independent variable at a time, omitting the influence of the others,[4-6] generating inaccurate results and requiring many experiments. To compensate for this, the response surface methodology (RSM) arises, a modeling technique used in the chemical, pharmaceutical[7] and food industries, biological and medical sciences,[1] inconstruction, manufacturing and soil mechanics,[3] due to its versatility,[8] since it can evaluate multiple independent variables and even their interaction, essential to know their additive, synergic and/or antagonistic effects on one or more responses,[9-12] very useful for predictions and process improvements,[13, 14] and a better interpretation.[15] Additionally, for its application it is sufficient to have a minimum number of experiments, without affecting the results.[16-18] In addition, when generating a mathematical equation, it can be validated to confirm its effectiveness.[19]

In recent years, the application of RSM in food processes has been extensively studied and, despite promising results, optimization in this field remains a challenge due to the complexity and dynamics of the products. In this context, the objective of this review is to analyze the current state of RSM in the extraction of agri-food compounds, previously knowing the fundamentals to understand the technique. In addition, the disadvantages and limitations of the technique will be determined, which is essential to know in order to avoid possible negative effects on the results.

Fundamentals of RSM

In an experimental design, there are independent variables or also called factors, which have an influence on the dependent or response variables. The standard equation (Eq.) (1) to find the response of interest (y) is given by the different factors (x), with their respective coefficients (f), in addition to an estimated error value (ε).[1]

$$y = f(x_1, x_2, x_3, \ldots, x_k) + \varepsilon \quad \ldots(1)$$

For a better analysis, the values of each factor are coded and standardized,[17] with values that generally oscillate between -1 and +1,[20] following the Eq. (2), where the coded variable (X) is generated from the actual variable (x) with its minimum and maximum value (or level).

$$X = \frac{x - \left(\frac{x_{max} + x_{min}}{2}\right)}{\left(\frac{x_{max} + x_{min}}{2}\right)} \quad \ldots(2)$$

Steps for RSM Application

The steps, based on the proposals of different researchers,[1, 2, 8, 11, 14, 17, 20] have been synthesized in a concise way, divided into four stages (Figure 1).

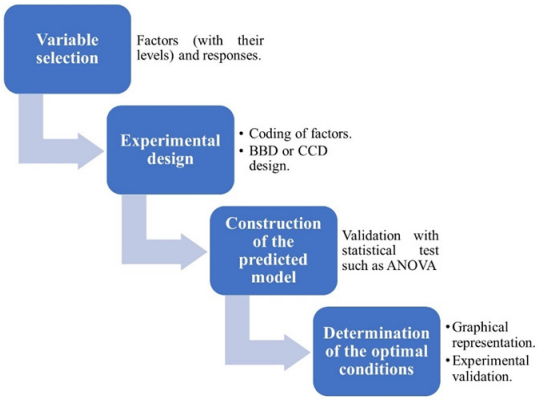

Fig.1: RSM flowchart

A crucial step is the statistical validation of the model. If it is not adequate, the irrelevant factors must be filtered out and the experimental runs must be repeated.

Identification of Variables

The main step is to establish the dependent and independent variable(s), determining significant factors to reduce the number of experiments and improve modeling.[17, 18, 20, 21]

Selection of A Response Surface Design

RSM is bases on Box-Behnken Design (BBD) and Central Composite Design (CCD),[11, 17, 19] among other derivates such as Face-Centered CCD (FCCCD), Rotable CCD (RCCD),[20] Cube Style CCD (CSCCD) and Spherical CCD (SCCD).[2] BBD and CCD are 3^k and 5^k designs, respectively that provide 3 and 5 levels for each "k"or factor.[20-22] With Eq. (3) and Eq. (4) we obtain the number of experiments applying BBD and CCD, where C_0 is the number of central points set.[19]

$$N = 2k(k-1) + C_0 \quad ...(3)$$

$$N = 2^k + 2^k + C_0 \quad ...(4)$$

It is necessary to indicate that the designs are adjusted from Eq. (1) to first-degree and second-degree models, which, their form is given by Eq. (5) and Eq. (6), respectively, where x are the factors and β are their coefficients, β_0 is the intercept coefficient and ε is the error.[14] In addition, the model changesdue to the interactions, applying the Eq. (7), where β_0, β_i, β_{ii} and β_{ij} are the intercept, linear, quadratic and interaction coefficients.[6]

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + ...\beta_k x_k + \varepsilon \quad ...(5)$$

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_1 x_1^2 + \beta_2 x_2^2 + \varepsilon \quad ...(6)$$

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i \le i \le j}^{k} \beta_{ij} x_i x_j + \varepsilon \quad ...(7)$$

Construction and Evaluation of the Best Mathematical Model

When the model is selected, it must be statistically verified whether it correctly represents the relationship between the variables.[21] For this purpose, analysis of variance (ANOVA) is performed, which evaluates the precision of the predictive model through the coefficient of determination (R^2).[11] In addition, other techniques are also used, such as lack of fit test, mean absolute deviationand residual analysis. Due to the interest in optimizing the different responses of a food process, there is a multi-criteria methodology called desirability function[20] that combines the values of each partial desirability ($d_n Y_n$) to generate the overall desirability (D),[23] which is the geometric mean, according to Eq. (8).[24]

$$D = [(d_1 . Y_1)\,(d_2 . Y_2)\,...\,(d_n . Y_n)]^{\frac{1}{n}} \quad ...(8)$$

Model Plots and Determination of the Optimal Conditions

The next step is to generate the contour (two-dimensional) and surface (three-dimensional) response graphs to better observe the significant relationship between input and output variables.[12, 14] The valuesare estimated, but since they are as close as possible to the real ones, it is sufficient for a good interpretation.[20] Once the graphs have been obtained, the optimal conditions are determined using Eq. (9), considering that the optimum value is not necessarily the maximum;[17] for example, in the research of Louhichi *et al.*,[12] concerning the treatment of vegetable oil refinery wastewater, the objective was to achieve the lowest values of chemical oxygen demand and turbidity.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{12} x_1 x_2 \quad ...(9)$$

In the end, the validity of the generated equation must be confirmed. The difference between the predicted and experimental responses must be less than 5%.[20]

RSM in The Extraction of Agri-Food Compounds

In the food industry, RSM has been used in enzymatic hydrolysis, clarification,[1] metabolite production,[20] microencapsulation,[22, 25] product improvement and formulation,[26-28] in thermal treatments such as cooking,[23] non-thermal treatments such as osmotic drying[29] and plasma cold,[30-32] in wastewater treatment,[12, 16] in packaging,[22, 33, 34] in germination[35] and especially in the extraction of compounds,[19, 36] due to their properties and potential applications, mainly in the food and pharmacological fields.[37]

There are thermal extraction techniques or called conventional solid-liquid, but there are also non-thermal techniques, more efficient and they have less impact on food quality.[38] Regarding the compounds to be extracted, they can be polysaccharides, proteins, oils, pigments, hydrocolloids or polyphenols, which are the most studied.[39] Regardless of the extraction method or the target compound, determining the best process conditions is a tedious task[40] and, therefore, optimization with techniques such as RSM is indispensable. In this context, in recent years, the number of investigations on its application in this field has increased substantially.For a better analysis, a recent summary is shown in Table 1.

In the extraction there are many variables that affect the response(s); the most common are time, temperature, pH, type, concentration and proportion of the solvent.[5] There are also specific variables such as power in the case of microwave extraction. All the factors have an influence individually, but as mentioned, it is also essential to understand the effect of their interaction, in order to interpret the process as a whole. As shown in Table 1,

temperature is one of the most significant factors, but it is affected when its value is very high, which is a limitation; However, it is not inconvenient for emerging techniques such as vacuum-ultrasound assisted enzymatic extraction, pulsed electric fields assisted extraction and atmospheric cold plasm assisted extraction, in which other variables have a greater influence, such as enzyme concentration, pressure and power, which, in general, soften, permeabilize and break down the matrix tissues, facilitating mass transfer without the use of high temperatures.[41] Consequently, the compounds are not affected, increasing the extraction yield.

Table 1: Recent findings on application of RSM in the extraction of agri-food compounds

Compound (s) and matrix	Extraction method	Design	Parameters and validated results*	Key findings**
Proteins from defatted grape seed flour	Alkaline and isoelectric precipitation	BBD	pH: 10; t: 2h; T: 36 ºC; flour /water ratio: 1:9, getting 55.35 g protein/100g of concentrated protein, with R^2 of 0.8074.	pH was more significant, but if it increases too much, it negatively affects protein content. Its interaction with T is peculiar, when both increase, their individual effects are not significant.[5]
Polyphenols and flavonoids from corms of *Crocus sativus L.*	Direct with solvents	FCCD	t: 60 min; T:48 ºC; Ethanol: 80%, getting 89.28 y 100. 39 mg GAE/100 g dw, also of 0.912 and 1.558 mg QE/100 g dw, with R^2 of 0.9917 and 0.9727.	T was very influential up to 60°C and its simultaneous increase with time degraded the compounds. Aqueous ethanol solution was the best, due to its affinity with the low polarity of the polyphenols.[9]
Proteins and polyphenols from sesame bran	Vacuum-ultrasound assisted enzymatic	CCD	t: 8 min y 68 min of restoration; EC: 1.82 AU/100 g; p: 238 mmHg, getting 1707.66 mg GAE/100 g dw, with R^2 of 0.9726 and 0.9791.	The interaction between pressure-restoration time had a direct influence on the response. The restoration time-EC effect was negative; if one increases, the other should decrease.[36]
Polyphenols from green tea leaves	Atmospheric cold plasm assisted	FCCCD	t of PT: 15 min; t: 30 min; T: 80 ºC; P: 15 W, Φ of nitrogen: 1.5 L/min, getting 913.894 mg GAE/g of dry weight, with R^2 of 0.944.	PT with cold plasm increased the yield by 41.14% due to the interaction between P-t of PT, which caused the softening and rupture of plant tissues, allowing a higher recovery of polyphenols.[38]
Polyphenols and soluble proteins from *Momordica charantia*	Ultrasound (normal and pulsed) assisted	SCCD	t: 11.6 min; T: 68.4 ºC; sample/water ratio: 0.3 g/L, getting 103.4 and 104.5 mg GAE/g, and 46.2 and 42.1 mg of protein/L, in normal and pulsed model, with R^2 of 0.9955 and 0.9635.	T favored the mass transfer of the compounds to the extract. In the pulsed mode, time had greater influence because at prolonged pulsations, cavitation bubbles increase, bursting in the cell wall and facilitating the release of the compounds.[42]
Scopoletin, rutin and alizarin from noni	High hydrostatic pressure	BBD	t: 15 min; ethanol: 65%; p: 544 MPa, getting a yield of 82.4, 77.2 and 82.2 %, with R^2 of 0.9908, 0.9506 and 0.9966.	Pressure had a significant effect individually; however, its interaction with ethanol concentration was negative.[43]
Lutein from	Maceration	CCD	t: 4 h; T: 42.4 ºC; methanol:	The two-way and three-way

Tetraselmis suecica			100%; sample/water ratio: 1.25 g/L of biomass, getting 9.948 mg GAE/g and 1.422 mg RUT/g of fresh weight, with R^2 of 0.9831.	interaction between t-T and sample/water ratio was directly proportional to the lutein content, until T approached 60ºC.[44]
Polyhenols from chestnut shell	Subcritical water	CCD	t: 30 min; T: 220 ºC, water/sample ratio: 10:1, getting 405.87 mg GAE/g dw, with R^2 of 0.7436.	t-T influenced individually and interactively up to about 100°C, but above 150°C, the phenol content increased significantly again.[45]
Cassava starch	Ultrasound assisted	BBD	t: 10min; water/sample ratio: 30:1; P: 90%; pulse cycle: 1/s, getting 56.57% of starch, with R^2 of 0.9522.	Water/sample ratio was the most significant, being negative when exceeding 30:1. The interaction between P-pulse cycle was very positive, increasing cavitation for starch release.[46]
Pectin from Passiflora edulis peels	Microwave assisted	BBD	pH: 2.9; t: 12 min; water/sample ratio: 57 mL/g; P: 218 W, getting 18.73% of yield, with R^2 of 0.9741.	The interaction between P-t showed negative trends after 12 minutes, due to the indirect increase in T. The acidic medium hydrolyzed protopectin, a precursor that facilitated solubilization and extraction of soluble pectin. Additional, the high volume of water caused rapid hydration, swelling and rupture of the tissues, releasing pectin.[47]
Pectin from *Punica granatum L.* peel	Supercritical fluid	BBD	t: 2.5 h; T: 46.5 ºC; p: 291 bar; Φ of CO2: 2 L/min, getting mg of galacturonic acid/g AIR, with R^2 of 0.74.	Pressure increased the density of CO^2 and its efficiency in the solubility of the extract; therefore, it was not necessary to increase time and T because it affected the yield.
Polyphenols from potato peels	Pulsed Electric Fields (PEF) assisted	FCCCD	t of PT: 230 min; t: 240 min T: 50 ºC; ethanol: 52%; solvent/sample ratio: 20 mL/g, getting 1295 mg GAE/g of fresh weight, with R^2 of 0.9907.	PT with PEF increased yield by 10%. In addition, it decreased the influence of time, but increased the effect of ethanol and its interaction with T.[49]

T: temperature; t: time; p: pressure; P: power; GAE: gallic acid equivalent; QE: quercetin dihydrate equivalent; dw: dry weight; EC: enzyme concentration; AU: alcalasa activity; PT: pretreatment; AIR: alcohol-insoluble residues. *All models were second-degree.**Greater significance between the factors and their interactions.

Some characteristics resulting from the conditioning of the raw material, such as particle size and shape after grinding, can also be considered as a factor.[40] In this sense, Chanioti *et al*.[13] evaluated the influence of particle size of olive pomace in the ultrasoundassisted extraction of oil, unsaponifiable matter and polyphenols. The optimal conditions using BBD were at 60ºC, sample/n-hexane ratio of 1:12 and 0.5 mm of particle, recovering 11.03% of oil; for the unsaponifiable matter, only at 55ºC was obtained 4.5%; regarding the content of total phenols, which was 0.261 mg GAE/g of oil, it was obtained at 50ºC, with a solid-liquid ratio of 1:8 and 0.9 mm of particle.

In other study, Ishak *et al*.[50] obtained 30.7% of oil from chia by optimizing with CCD thesupercritical fluid extraction at 45ºC, 335 bar, 24 s of grinding time and 100−400 µm of particle. According to Rivas *et al*.[48] when the particles are small, the solvent passes faster through the tissues, avoiding the innate resistance to mass transfer.

As is known, the extraction of compounds from agro-industrial by-products is common, which represent approximately 30% of the food[51] and which are usually discarded,[5] but their use affects the sustainability of the industry, reducing environmental pollution and its impact. In addition, they mainly contain antioxidants with pharmacological activity, such as polyphenols, but their yield is very low and therefore it is essential to optimize their recovery.[52] García *et al*.[53] evaluated pressurized liquid extraction of phenols and punicalagin from pomegranate peel. They optimized it with a CCD at 200ºC and using 77% ethanol, recovering 164.3 mg GAE/g and 17 mg of punicalagin/g dw.

Another important point is the application of the extracted compounds, especially as natural additives in other food processes. Roy *et al*[54] optimized the ultrasound assisted extraction of astaxanthinfrom the shrimp shell using deep natural eutectic solvents with a BBD. With 39 min, an amplitude of 54.43%, the HBD/HBA ratio (molar ratio of the donation of hydrogen bonds and acceptance of lactic acid) of 1:1.02, it was obtained 68.98 mg/g dw. Additionally, it was used as a plasticizer for biofilms based on chitosan, achieving high DPPH(1,1-difenil-2 picrilhidrazilo) antioxidant activity, better sensory, physical, mechanical and thermal characteristics.
Finally, extraction can focus on biological activities. Pinto *et al*.[51] optimized the production of an extract with a high antioxidant potential from Castaneasativa shell using supercritical CO_2. With a CCD at 60ºC, 350 bar and 15% of ethanol as cosolvent, the antioxidant activity by DPPH assay was of 54.91%, with an R^2 of 84.817%. Subsequently, the extract was able to eliminate cancer cell lines such as Caco-2 (477.94 g/mL) and HT29-MTX (3.71 g/mL).

It is important to note that RSM can be used simultaneously with other techniques to improve optimization,[55] such as artificial neural networks (ANNs), related to the networks of the human brain. It is better in complex non-linear processes.[7] Ciric *et al*.[6] used RSM-ANNs to improve the ultrasound assisted extraction of polyphenols and flavonoids from *Allium sativum L*. The best parameters were at 59ºC, for 13.5 min, using 71% methanol as solvent in a ratio of 20:1 with the sample, obtaining 19.948 mg GAE and 1.422 mg routine equivalent/g of fresh weight, with 0.9998 and 0.9885 of adjusted R^2, respectively. According to research of Rebollo-Hernanz *et al*.[7] on the conventional extraction of polyphenols from coffee husk, RSM is first used to run the experimental runs quickly and to build and adjust the mathematical model (R^2: 0.9402) that serves as the basis for ANNs; it analyzes and predicts mainly quadratic interactions, obtaining a new and more accurate model (R^2: 0.9802). Considering another technique such as fuzzy logic (FL). Khamparia *et al*.[56] compared RSM, ANNs and FL in the conventional extraction of oleonolic acid from *Ocinum sanctum*, concluding that ANNs was better, followed by RSM and FL, with R^2 values of 0.994, 0.992 and 0.703.

Regarding other methods, Sodeifian *et al*.[57] optimized the supercritical CO_2 extraction of essential oil from Eryngium billardieriwith RSM and simulated annealing (SA), a useful algorithm for a better global optimization from the improvement of each factor. From the data obtained with RSM, thanks to SA, the kinetic behavior of the process was described, and the model was adjusted and reoptimized. A maximum yield of 0.8522% of essential oil was obtained, at 300 bar, 35ºC, 130 min and with 0.75 mm of particle size. Similarly, Vásquez-Villalobos *et al*.[58] optimized the conventional extraction of glucosinolates from maca (Lepidium meyenii) using RSM. They could not obtain the optimal value due to limitations of the technique, but they complemented it with genetic algorithm (GA) and finally managed to obtain a maximum of 17.1 µmol ofglucosinolates/g of fresh weight, using ethanol (70.95%), sample/ solvent ratio of 10:1,at 78.98 ºC and for 90 min.

Current and Future Challenges

To apply RSM, a series of steps must be carefully followed. For this, it is essential to have experience in the subject or a basic notion from previous studies, in order to make the correct choice of data and that these are close to the desired optimization; otherwise, if the range of values selected is not adequate, the results will not be as expected and,

therefore, the optimization will not occur in the best conditions.

Regarding the selection of the best mathematical model, it is advisable to choose for the model with the lowest degree, but that this is statistically significant. In most cases, second-degree equations are usually used, however, these do not usually represent the database and, therefore, the predicted values tend to be relatively far from the experimental ones.[2] The main disadvantage of RSM is that the data are fitted to a second degree polynomial model due to the presence of curvatures in the process, which is incorrect because there may also be curvatures in higher degree models and even more so when considering the complexity of the extraction processes. To solve these limitations, as previously determined, RSM can be complemented with other optimization techniques such as ANNs, FL, SA and GA. Another advantage of these combinations is that with the correct description of the process dynamics, simulations can be performed, which is a current trend. This would make it possible to run an infinite number of experiments virtually, considerably reducing time and costs.

Conclusions

The application of RSM requires basic knowledge of experimental design, modeling and data validation. Currently, it is being widely used in the optimization of the extraction of bioactive compounds in the food industry, including polyphenols, carbohydrates, proteins and oils from a variety of agri-food products and using multiple extraction techniques, demonstrating the versatility and suitability of RSM. Also, according to the literature, RSM has limitations, but they can be corrected with other optimization tools, in addition to offering an enhanced technique that provides better results.

Gratitude

Declared none.

Funding

This work is a self-funded thus nothing to declare.

Conflict of Interest

The author(s) declares no conflict of interest.

References

1. Malekjani N., Jafari S.M. Food Process Modeling and Optimization by Response Surface Methodology (RSM). In: Sevda S., Singh A. (Editors.). *Mathematical and Statistical Applications in Food Engineering.* Florida: CRC Press, 2020: 181-203.
2. Aydar A. Statistical Methods in Optimization of Food Materials. *Eur. Int. J. Sci. Technol.* 2019;8(3):33-40.
3. Myers R.H., Montgomery D.C., Anderson-Cook C.M. Response Surface Methodology: Process and product optimization using designed experiments. Fourth edition. United States: Wiley, 2016.
4. Bezerra M.A., Santelli R.E., Oliveira E.P., Villar L.S., Escaleira L.A. Response surface methodology (RSM) as a tool for optimization in analytical chemistry. Talanta. 2008,76:965-977.
5. Baca-Bocanegra B., Nogales-Bueno J., Hernández-Hierro J.M., Heredia F.J. Optimization of Protein Extraction of Oenological Interest from Grape Seed Meal Using Design of Experiments and Response Surface Methodology. Foods. 2021;10(1):79.
6. Ciric A., Krajnc B., Heath D., Ogrinc N. Response surface methodology and artificial neural network approach for the optimization of ultrasound-assisted extraction of polyphenols from garlic. *Food Chem. Toxicol.* 2020,135:110976.
7. Rebollo-Hernanz M., Cañas S., Taladrid D., Segovia A., Bartolomé B., Aguilera Y., Martín-Cabrejas M.A. Extraction of phenolic compounds from cocoa shell: Modeling using response surface methodology and artificial neural networks. *Sep.Purif.Technol.* 2021;270:118779.
8. Baş D., Boyac I.H. Modeling and optimization I: Usability of response surface methodology. *J. Food Eng.* 2007,78(3):836-845.
9. Esmaeelian M., Jahani M., Feizy J. &

Einafshar S. Effects of Ultrasound-Assisted and Direct Solvent Extraction Methods on the Antioxidant and Antibacterial Properties of Saffron (Crocus sativus L.) *Corm Extract. Food Anal. Methods.* 2021;14:74-87.

10. Nwabueze T.U. Basic steps in adapting response surface methodology as mathematical modelling for bioprocess optimisation in the food systems. *Int. J. Food Sci. Technol.* 2010;45:1768-1776.
11. Said K.A.M., Amin M.A.M. Overview on the Response Surface Methodology (RSM) in Extraction Processes. *J. Appl. Sci. Process Eng*. 2016;2(1):8-16.
12. Louhichi G., Bousselmi L., Ghrabi A., Khouni I. Process optimization via response surface methodology in the physico-chemical treatment of vegetable oil refinery wastewater. *Environ. Sci. Pollut. Res*. 2019;26:18993-19011.
13. Chanioti S., Tzia C. Optimization of ultrasound-assisted extraction of oil from olive pomace using response surface technology: Oil recovery, unsaponifiable matter, total phenol content and antioxidant activity. LWT. 2017;79:178-189.
14. Özbek H.N. Yanık D.K. Fadıloğlu S., Göğüş F. (2020). Optimization of microwave-assisted extraction of bioactive compounds from pistachio (Pistacia vera L.) *hull. Sep. Sci. Technol*. 2020;55(2):289-299.
15. Ryu D.H., Cho J.Y., Sadiq N.B., Kim J.C., Lee B., Hamayun M., Lee T.S., Kim H.S., Park S.H., Nho C.W. Optimization of antioxidant, anti-diabetic, and anti-inflammatory activities and ganoderic acid content of differentially dried Ganoderma lucidum using response surface methodology. *Food Chem*. 2021;335:127645.
16. Abdulgader M., Yu Q.J., Zinatizadeh A.A., Williams P., Rahimi, Z. Application of response surface methodology (RSM) for process analysis and optimization of milk processing wastewater treatment using multistage flexible fiber biofilm reactor. *J. Environ. Chem. Eng*. 2020;8(3):103797.
17. Nair A.T. Makwana A.R., Ahammed M.M. The use of response surface methodology for modelling and analysis of water and wastewater treatment processes: a review. *Water Sci. Technol*. 2014;69(3):464-478.
18. Oberoi D.P.S., Sogi D.S. Utilization of watermelon pulp for lycopene extraction by response surface methodology. *Food Chem.* 2017;232:316-321.
19. Ferreira S.L.C., Junior M.M.S., Felix C.S.A., da Silva D.L.F., Santos A.S., Neto J.H.S., De Souza C.T., Junior R.A.C., Souza A.S. Multivariate optimization techniques in food analysis - A review. *Food Chem.* 2019;273:3-8.
20. Yolmeh M., Jafari S.M. Applications of Response Surface Methodology in the Food Industry Processes. *Food Bioproc. Tech*. 2017;10:413-433.
21. Khuri A.I. Response surface methodology and its applications in agricultural and food sciences. *Biom. Biostat. Int.J*. 2017;5(5):155-163.
22. Bazaria B., Kumar P. Optimization of spray drying parameters for beetroot juice powder using response surface methodology (RSM). *J. Saudi Soc. Agric. Sci.* 2016;17(4):408-415.
23. Aghajanzadeh S., Ziaiifar A.A., Kashaninejad M. Influence of thermal treatment, homogenization and xanthan gum on physicochemical properties of watermelon juice: A response surface approach. LWT. 2017;85(A):66-74.
24. DePalma K., Smith B., McDonald A.G. Synergistic effects of processing parameters on the biochemical and physical properties of tofu made from yellow field pea (Pisum sativum), as determined by response surface methodology. *Food Sci. Nutr.* 2021;9:1132-1142.
25. Vivek K., Mishra S., Pradhan R.C. Optimization of Spray Drying Conditions for Developing Nondairy Based Probiotic Sohiong Fruit Powder. *Int. J. Fruit Sci.* 2021;21(1):193-204.
26. Botinestean C., Hossain M., Mullen A.M., Auty M.A.E., Kerry J.P., Hamill R.M. Optimization of textural and technological parameters using response surface methodology for the development of beef products for older consumers. *J. Texture Stud*. 2020;51:263-275.
27. Benkadri S., Salvador A., Sanz T., Zidoune M.N. Optimization of Xanthan and Locust Bean Gum in a Gluten-Free Infant Biscuit Based on Rice-Chickpea Flour Using Response Surface Methodology. *Foods*. 2021;10(1):12.

28. Hosseini A.F. Mazaheri-Tehrani M., Yeganehzad S., Razavi S.M.A. Providing new formulation for white compound chocolate based on mixture of soy flour, sesame paste, and emulsifier: An optimization study using response surface methodology. *Food Sci. Nutr.* 2021;9:1432-1440.
29. Salimi A., Hoseinnia F. Optimization of coconut osmotic drying preceded by microwave treatment by Response Surface Methodology. *Brazilian J. Food Technol.* 2020;23:e2018249.
30. Intanon W., Vichiansan N., Leksakul K., Boonyawan D., Kumla J., Suwannarach N., Lumyong S. Inhibition of the aflatoxin-producing fungus Aspergillus flavus by a plasma jet system. *J. Food Process. Preserv.* 2020;45:e15045.
31. Katsigiannis A.S., Bayliss D.L., Walsh J.L. Cold plasma decontamination of stainless steel food processing surfaces assessed using an industrial disinfection protocol. *Food Control.* 2021;121:107543.
32. Zhuang H., Rothrock Jr M.J., Line J.E., Lawrence K.C., Gamble G.R., Bowker B.C., Keener K.M. Optimization of in-package cold plasma treatment conditions for raw chicken breast meat with response surface methodology Innov. *Food Sci. Emerg. Technol*. 2020;66:102477.
33. Marvdashti L.M., Ayatollahi S.A., Salehi B., Sharifi-Rad J., Abdolshahi A., Sharifi-Rad R., Maggi F. Optimization of edible Alyssum homalocarpum seed gum-chitosan coating formulation to improve the postharvest storage potential and quality of apricot (Prunus armeniaca L.). *J. Food Saf.* 2020;40:e12805.
34. Noorbakhsh-Soltani, S.M., Zerafat, M.M. & Sabbaghi, S. (2018). A comparative study of gelatin and starch-based nano-composite films modified by nano-cellulose and chitosan for food packaging applications. *Carbohydr. Polym*. 2018;189:48-55.
35. Ruiz-Hernández A.A., Cárdenas-López J.L., Cortez-Rocha M.O., González-Aguilar G.A., Robles-Sánchez R.M. Optimization of germination of white sorghum by response surface methodology for preparing porridges with biological potential. *CYTA J. Food*. 2021;19(1):49-55.
36. Görgüç A., Özer P., Yılmaz F.M. Simultaneous effect of vacuum and ultrasound assisted enzymatic extraction on the recovery of plant protein and bioactive compounds from sesame bran. *J. Food Compos. Anal.* 2020;87:103424.
37. Almusallam I.A., Ahmed I.A.M., Babiker E.E., Al Juhaimy F.Y., Fadimu G.J., Osman M.A., Al Maiman S.A.A., Ghafoor K., Alqah H.A.S. Optimization of ultrasound-assisted extraction of bioactive properties from date palm (Phoenix dactylifera L.) spikelets *using response surface methodology.* LWT.2021;140:110816.
38. Keshavarzi M., Najafi G., Gavlighi H.A., Seyfi P., Ghomi H. Enhancement of polyphenolic content extraction rate with maximal antioxidant activity from green tea leaves by cold plasma. *J. Food Sci.* 2020;85:3415-3422.
39. Kumar M., Dahuja A., Tiwari S., Punia S., Tak Y., Amarowicz R., Bhoite A.G., Singh S., Joshi S., Panesar P.S., Saini R.P., Pihlanto A., Tomar M., Sharifi-Rad J., Kaur C. Enhancement of polyphenolic content extraction rate with maximal antioxidant activity from green tea leaves by cold plasma. *Food Chem*. 2021;353:129431.
40. Belwal T., Ezzat S.M., Rastrelli L., Bhatt I.D., Daglia M., Baldi A., Devkota H.P., Orhan I.E., Patra J.K., Das G., Anandharamakrishnan C., Gomez-Gomez L., Nabavi S.F., Nabavi S.M., Atanasov A.G. A critical analysis of extraction techniques used for botanicals: Trends, priorities, industrial uses and optimization strategies. *Trends Analyt. Chem.* 2018;100:82-102.
41. Gagneten M., Leiva G., Salvatori D., Schebor C., Olaiz N. Optimization of Pulsed Electric Field Treatment for the Extraction of Bioactive Compounds from Blackcurrant. *Food Bioproc. Tech.* 2019;12:1102–1109.
42. Chakraborty S., Uppaluri R., Das C. Optimization of ultrasound-assisted extraction (UAE) process for the recovery of bioactive compounds from bitter gourd using response surface methodology (RSM). *Food Bioprod. Process.* 2020;120:114-122.
43. Jamaludin R ., Kim D.S., Salleh L.M., Lim S.B. Optimization of high hydrostatic pressure extraction of bioactive compounds from noni fruits. *J. Food Meas. Charact.* 2020;14:2810-

2818.

44. Lee K.H., Kim H., Ki J.S., Yoo H.Y. Optimization of Lutein Recovery from Tetraselmis suecica by Response Surface *Methodology. Biomolecules.* 2021;11(2):182.
45. Pinto D., Vieira E.F., Peixoto A.F., Freire C., Freitas V., Costa P., Delerue-Matos C., Rodrigues F. Optimizing the extraction of phenolic antioxidants from chestnut shells by subcritical water extraction using response surface methodology. *Food Chem.* 2021;334:127521.
46. Setyaningsih W., Fathimah K.R.N., Cahyanto M.N. Process Optimization for Ultrasound-Assisted Starch Production from Cassava (Manihot esculenta Crantz) Using Response Surface Methodology. *Agronomy.* 2021;11(1):117.
47. Dao T.A.T., Webb H.K., Malherbe F. Optimization of pectin extraction from fruit peels by responsesurface method: Conventional versus microwave-assisted heating. *Food Hydrocoll.* 2021;113:106475.
48. Rivas M.A., Casquete R., Córdoba M.G., Benito M.J., Hernández A., Ruiz-Moyano S., Martín A. Functional properties of extracts and residual dietary fibre from pomegranate (Punica granatum L.) peel obtained with different supercritical fluid conditions. LWT. 2021;145:111305.
49. Frontuto D., Carullo D., Harrison S.M., Brunton N.P., Ferrari G., Lyng J.G., Pataro G. Optimization of Pulsed Electric Fields-Assisted Extraction of Polyphenols from Potato Peels Using Response Surface Methodology. *Food Bioproc. Tech.* 2019;12:1708-1720.
50. Ishak I., Hussain N., Coorey R., Ghani M.A. Optimization and characterization of chia seed (Salvia hispanica L.) oil extraction using supercritical carbon dioxide. *J. CO_2 Util.* 2021;45:101430.
51. Pinto D., Cádiz-Gurrea M.L., Sut S., Ferreira A.S., Leyva-Jimenez F.J., Acqua S.D., Segura-Carretero A., Delerue-Matos C., Rodrigues F. Valorisation of underexploited Castanea sativa shells bioactive compounds recovered by supercritical fluid extraction with CO2: A response surface methodology approach. *J. CO2 Util.* 2020;40:101194.
52. Silva G.F.P., Pereira E., Melgar B., Stojkovic D., Sokovic M., Calhelha R.C., Pereira C., Abreu R.M.V., Ferreira I.C.F.R., Barros, L. Eggplant Fruit (Solanum melongena L.) and Bio-Residues as a Source of Nutrients, Bioactive Compounds, and Food Colorants, Using Innovative Food Technologies. *Appl. Sci.* 2021;11(1):151.
53. García P., Fredes C., Cea I., Lozano-Sánchez J., Leyva-Jiménez F.J., Robert P., Vergara C., Jimenez P. Recovery of Bioactive Compounds from Pomegranate (Punica granatum L.) Peel Using Pressurized Liquid Extraction. Foods. 2021;10(1):203.
54. Roy V.C., Ho T.C., Lee H.J., Park J.S., Nam S.Y., Lee H., Getachew A.T., Chun B.S. Extraction of astaxanthin using ultrasound-assisted natural deep eutectic solvents from shrimp wastes and its application in bioactive films. *J. Clean. Prod.* 2021;284:125417.
55. Banga J.R., Canto E.B., Moles C.G., Alonso A.A. Improving food processing using modern optimization methods. *Trends Food Sci. Technol.* 2003;13:131-144.
56. Khamparia A., Pandey B., Pandey D.K., Gupta D., Khanna A., de Alburqueque V.H.C. Comparison of RSM, ANN and Fuzzy Logic for extraction of Oleonolic Acid from Ocimum sanctum. *Comput. Ind.* 2020;117:103200.
57. Sodeifian G., Sajadian S.A., Ardestani N.S. Experimental optimization and mathematical modeling of the supercritical fluid extraction of essential oil from Eryngium billardieri: Application of simulated annealing (SA) algorithm. *J. Supercrit. Fluids.* 2017;127:146-157.
58. Vásquez-Villalobos V., Rojas-Padilla C., Rojas-Naccha J., Hernández-Bracamonte O., Vásquez-Angulo J., Barreto-Alama O. Optimización de la extracción de glucosinolatos de maca (Lepidium meyenii) por superficie de respuesta y algoritmos genéticos. *Sci. Agropecu.* 2016;7:275-284.