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

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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.

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
methods with scientific validity\textsuperscript{1, 2} that help predict the behavior of the variables of interest.\textsuperscript{3} Before the 1950s, techniques were used that only analyzed one independent variable at a time, omitting the influence of the others,\textsuperscript{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\textsuperscript{7} and food industries, biological and medical sciences,\textsuperscript{1} in construction, manufacturing and soil mechanics,\textsuperscript{3} due to its versatility,\textsuperscript{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,\textsuperscript{9-12} very useful for predictions and process improvements,\textsuperscript{13, 14} and a better interpretation.\textsuperscript{15} Additionally, for its application it is sufficient to have a minimum number of experiments, without affecting the results.\textsuperscript{16-18} In addition, when generating a mathematical equation, it can be validated to confirm its effectiveness.\textsuperscript{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).\textsuperscript{1}

\[
y = f(x_1, x_2, x_3, \ldots, x_n) + \varepsilon \quad \ldots (1)
\]

For a better analysis, the values of each factor are coded and standardized,\textsuperscript{17} with values that generally oscillate between -1 and +1,\textsuperscript{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).

\[
x = \frac{x_{\text{max}} + x_{\text{min}}}{2} \quad \ldots (2)
\]

**Steps for RSM Application**

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

![RSM flowchart](image)

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.\textsuperscript{17, 18, 20, 21}

**Selection of A Response Surface Design**

RSM is based on Box-Behnken Design (BBD) and Central Composite Design (CCD),\textsuperscript{11, 17, 18} among other derivatives such as Face-Centered CCD (FCCCD), Rotable CCD (RCCD),\textsuperscript{20} Cube Style CCD (CSCCD) and Spherical CCD (SCCD).\textsuperscript{2} BBD and CCD are 3^k and 5^k designs, respectively that provide 3 and 5 levels for each “k” or factor.\textsuperscript{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.\textsuperscript{19}
\[ N = 2k (k-1) + C_0 \] ... (3)

\[ N = 2^k + 2^k + C_0 \] ... (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 \( \beta \) are their coefficients, \( \beta_0 \) is the intercept coefficient and \( \epsilon \) is the error. In addition, the model changes due to the interactions, applying the Eq. (7), where \( \beta_0, \beta_i, \beta_{ii} \) and \( \beta_{ij} \) are the intercept, linear, quadratic and interaction coefficients.

\[ y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots \beta_k x_k + \epsilon \] ... (5)

\[ y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \ldots \beta_k x_k + \epsilon \] ... (6)

\[ y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<s,j}^{k} \beta_{ij} x_i x_j + \epsilon \] ... (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. For this purpose, analysis of variance (ANOVA) is performed, which evaluates the precision of the predictive model through the coefficient of determination \( (R^2) \). In addition, other techniques are also used, such as lack of fit test, mean absolute deviation and residual analysis. Due to the interest in optimizing the different responses of a food process, there is a multi-criteria methodology called desirability function that combines the values of each partial desirability \( (d_{iY_i}) \) to generate the overall desirability \( (D) \), which is the geometric mean, according to Eq. (8).

\[ D = \left( \prod_{i=1}^{n} d_{iY_i} \right)^{1/n} \] ... (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. The values are estimated, but since they are as close as possible to the real ones, it is sufficient for a good interpretation. Once the graphs have been obtained, the optimal conditions are determined using Eq. (9), considering that the optimum value is not necessarily the maximum; for example, in the research of Louhichi et al., concerning the treatment of vegetable oil refinery wastewater, the objective was to achieve the lowest values of chemical oxygen demand and turbidity.

\[ y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{12} x_1 x_2 \] ... (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%.

**RSM in The Extraction of Agri-Food Compounds**

In the food industry, RSM has been used in enzymatic hydrolysis, clarification, metabolite production, microencapsulation, product improvement and formulation, in thermal treatments such as cooking, non-thermal treatments such as osmotic drying and plasma cold, in wastewater treatment, in packaging, in germination and especially in the extraction of compounds, due to their properties and potential applications, mainly in the food and pharmacological fields.

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. Regarding the compounds to be extracted, they can be polysaccharides, proteins, oils, pigments, hydrocolloids or polyphenols, which are the most studied. Regardless of the extraction method or the target compound, determining the best process conditions is a tedious task 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. 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. 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 R² 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. T was very influential up to 60 ºC 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. 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. 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. 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. Pressure had a significant effect individually; however, its interaction with ethanol concentration was negative. 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 R² of 0.9831. Interaction between t-T and sample/water ratio was directly proportional to the lutein content, until T approached 60°C.44

Polyphenols from chestnut shell

Subcritical water CCD t: 30 min; T: 220 °C, water/sample ratio: 10:1, getting 405.67 mg GAE/g dw, with R² 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 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

Cassava starch

Ultrasound assisted BBD t: 10min; water/sample ratio: 30:1; P: 90%; pulse cycle: 1/s, getting 56.57% of starch, with R² of 0.9522.

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 R² of 0.9741.

Pectin from Punica granatum L. peel

Supercritical fluid BBD t: 2.5 h; T: 46.5 °C; p: 291 bar; Φ of CO2: 2 L/min, getting mg of galacturonic acid/g AIR, with R² of 0.74.

Polyphenols from potato peels

Pulsed Electric Fields (PEF) assisted FCCCD t of PT: 230 min; t: 240 min T: 50 °C; ethanol: 52%; solvent/sample ratio: 20 mL/g, getting 1295 mg GAE/g of fresh weight, with R² 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.50 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 60°C, sample/n-hexane ratio of 1:12 and 0.5 mm of particle, recovering 11.03% of oil; for the unsaponifiable matter, only at 55°C was obtained 4.5%; regarding the content of total phenols, which was 0.261 mg GAE/g of oil, it was obtained at 50°C, with a solid-liquid ratio of 1.8 and 0.9 mm of particle.
In other study, Ishak et al.\textsuperscript{50} obtained 30.7% of oil from chia by optimizing with CCD the supercritical fluid extraction at 45°C, 335 bar, 24 s of grinding time and 100–400 μm of particle. According to Rivas et al.\textsuperscript{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\textsuperscript{51} and which are usually discarded,\textsuperscript{6} 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.\textsuperscript{52} Garcia et al.\textsuperscript{53} evaluated pressurized liquid extraction of phenols and punicalagin from pomegranate peel. They optimized it with a CCD at 200°C 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.\textsuperscript{54} optimized the ultrasound assisted extraction of astaxanthin from 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.\textsuperscript{51} optimized the production of an extract with a high antioxidant potential from Castaneasativa shell using supercritical CO\textsubscript{2}. With a CCD at 60°C, 350 bar and 15% of ethanol as cosolvent, the antioxidant activity by DPPH assay was of 54.91%, with an R\textsuperscript{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,\textsuperscript{55} such as artificial neural networks (ANNs), related to the networks of the human brain. It is better in complex non-linear processes.\textsuperscript{7} Ciric et al.\textsuperscript{6} used RSM-ANNs to improve the ultrasound assisted extraction of polyphenols and flavonoids from Allium sativum L. The best parameters were at 59°C, 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\textsuperscript{2}, respectively. According to research of Rebollo-Hernanz et al.\textsuperscript{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\textsuperscript{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\textsuperscript{2}: 0.9802).

Regarding other methods, Sodeifian et al.\textsuperscript{56} optimized the supercritical CO\textsubscript{2} extraction of essential oil from Eryngium billardierii with 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, 35°C, 130 min and with 0.75 mm of particle size. Similarly, Vázquez-Villalobos et al.\textsuperscript{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 °C 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. 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.

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Conflict of Interest
The author(s) declares no conflict of interest.

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