Mixture Designs in Beverages/Foods/Pharmaceutical Health

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Contributor: Diego Galvan

Design of Experiments (DoE) is a statistical tool used to plan and optimize experiments and is seen as a quality technology to achieve products excellence. Among the experimental designs (EDs), the mixture designs (MDs) stand out, being widely applied to improve conditions for processing, developing, or formulating novel products. Overall, the SOM indicated that Brazil presented the largest number of works using MDs. Among the continents, America and Asia showed a predominance in applications with the same amount of work. Comparing the MDs application areas, the analysis indicated that works are prevalent in food and beverage science in the American continent, while in Asia, health science prevails. MDs were more used to develop functional/nutraceutical products and the formulation of drugs for several diseases. However, we briefly describe some promising research fields in that MDs can still be employed.

Keywords: design of experiments (DoE) ; experimental designs (EDs) ; mixture designs (MDs) ; simplex lattice design (SLD) ; simplex-centroid design (SCD)

1. Introduction

Currently, food and health science studies are becoming more complex with a considerable increase in the number of variables, requiring robust methods for simultaneous data analysis [1]. These analyzes can be facilitated using mathematical and statistical fundamentals, known as chemometric methods, which can be divided into the design of experiments, multivariate data analysis, and multivariate calibration [2][3][4].

Design of Experiments (DoE) is a statistical tool used to plan and optimize experiments and is seen as a quality technology to achieve products excellence [5][6][7][8][9]. Among the various experimental designs (EDs), the mixture designs (MDs) stand out. In MDs, two or more components are mixed in different proportions, and the characteristics of the resulting products are recorded. The responses are independent of physical states, depending only on the proportions of the ingredients present in the mixtures [7][8][10][11].

In MDs, the response depends only on the mixture and not on the mixture's total amount. The sum of a mixture's proportions in different components or ingredients is always 1% or 100% [8][12]. In an experiment with q components, the proportions of the ingredients may be denoted by x1, x2, …, xq, where xi ≥ 0 for i = 1, 2, …, q and ∑qi=1xi=1, where xi represents the proportion of the i-th component. This equation removes a degree of freedom from the proportions and the factor space is, therefore, a (q − 1)-dimensional regular simplex [2][8][9][13].

$$\text{Linear}: \ \hat{y} = \sum_{i=1}^{q} \beta_i x_i \quad (1)$$

$$\text{Quadratic}: \ \hat{y} = \sum_{i=1}^{q} \beta_i x_i + \sum_{i<j}^{q-1} \sum_{j}^{q} \beta_{ij} x_i x_j \quad (2)$$

$$\text{Special cubic}: \ \hat{y} = \sum_{i=1}^{q} \beta_i x_i + \sum_{i<j}^{q-1} \sum_{j}^{q} \beta_{ij} x_i x_j + \sum_{i<j}^{q-2} \sum_{j<k}^{q-1} \sum_{k}^{q} \beta_{ijk} x_i x_j x_k \quad (3)$$

$$\text{Full cubic}: \ \hat{y} = \sum_{i=1}^{q} \beta_i x_i + \sum_{i<j}^{q-1} \sum_{j}^{q} \beta_{ij} x_i x_j + \sum_{i<j}^{q-1} \sum_{j}^{q} \delta_{ij} x_i x_j (x_i - x_j) + \sum_{i<j}^{q-2} \sum_{j<k}^{q-1} \sum_{k}^{q} \beta_{ijk} x_i x_j x_k \quad (4)$$

The parameter βi represents the expected response to the pure blend xi = 1 and xj = 0 when j ≠ i. The term ∑qi=1βixi represents the linear blending portion. When curvature arises from nonlinear blending between component pairs, the parameters βij, which represent either synergistic or antagonistic blending, will be different from zero [2][8].

Developing a novel product requires mixing two or more ingredients, and specific characteristics or restrictions are often desired [14]. Therefore, product formulation is still a challenge that has dogged chemists, pharmacists, and food scientists. Conventionally, product development requires much work and experiments, which increase with the number of variables evaluated. Furthermore, when experiments are based on trial and error, without an experimental design, there is the possibility of presenting low reproducibility, robustness, versatility, as they are not statistically validated [15].

In this sense, the use of MDs makes it possible to find the best proportion of these components through predictive equations that allow the application of mathematical algorithms, making it possible to determine the optimal conditions for a formulation or an industrial process [2][5][6][7][8][13][16]. The application of these models aims at high quality, low cost, and optimizes single or multiple responses simultaneously (applying desirability functions), and solves challenges with restrictions [5][6][7][16].

Improvements in food, beverage, and health processing techniques have been increasingly recurrent due to the general expectation for higher quality/quantity products today. Jointly, factors that ensure food security to these demands. Thus, MDs can facilitate the development of novel products or techniques that seek to achieve these goals. Among some typical applications, we can list the development of foods and beverages with functional or nutraceutical properties [14][17][18][19], while in the pharmaceutical health area, they are used to formulate drugs for several diseases [15][20][21]. In addition, MDs can also be used for many other applications [5][22][23].

A general representation for the MDs is through the figure of an equilateral triangle for systems with three components. The vertices correspond to the pure components and the sides to the binary mixtures, while the points located inside the triangle represent the mixtures of three components, called the central or centroid point [2][8][9]. The variation of a given property with a mixture's composition is represented by a response surface drawn above the triangle. Thus, the surface's representation can be done through a triangular diagram of contour lines [2][12].

Over the years, many MDs types have been developed for a specific purpose with extensive application in science, engineering, and industry [2][12]. Among the most common/used are the simplex lattice design (SLD) [9][11][13], simplex-centroid design (SCD) [9][13][24], simplex axial design (SAD) [9][13][25] and extreme vertex design (EVD) [9][13][26][27][28]. For more details, please see the Supplementary Material. Many works that employ designs for experiments with mixture followed the Scheffé regression models [5][6][7][13][16][29][30]. They can be extended to projects with more than three components [9][29]. The widespread models are represented in Equations (1)–(4).

2. Mixture Designs Applications

2.1. Application of Mixture Design around the World

Initially, all possible applications for MDs around the world were considered. According to the data set, **Figure 1** shows the countries and their continents that most used MDs in the beverage, food, pharmaceutical health, and other science in the last five years.

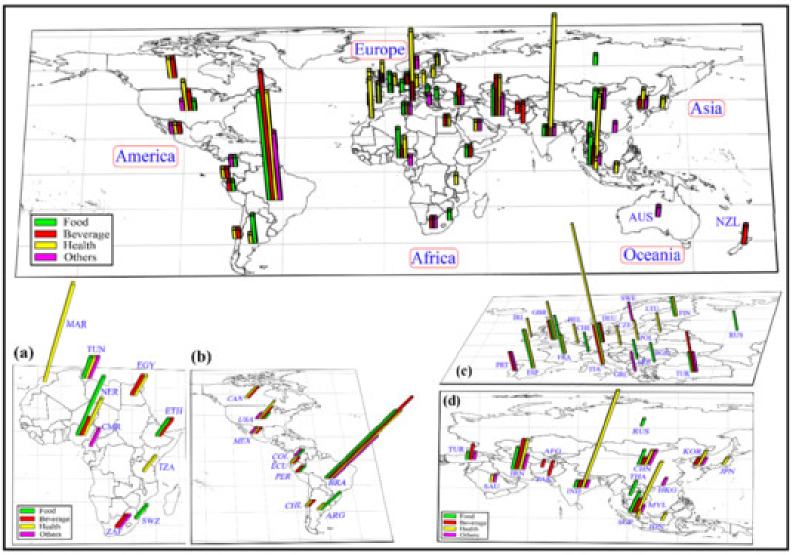

Figure 1. Application of mixture designs around the world between 2016 and 2020. Africa (**a**), America (**b**), Europe (**c**), and Asia (**d**).

2.2. Application of Mixture Design by Area

Overall, **Figure 2** shows that MDs have been increasingly applied in different areas of knowledge over the years, being more applied in the pharmaceutical health area, followed by the food and beverage areas. In this sense, researchers have applied MDs to improve processing conditions, new product development, or obtain unique sensory and physicochemical characteristics in products, among other numerous applications described briefly in the following sections.

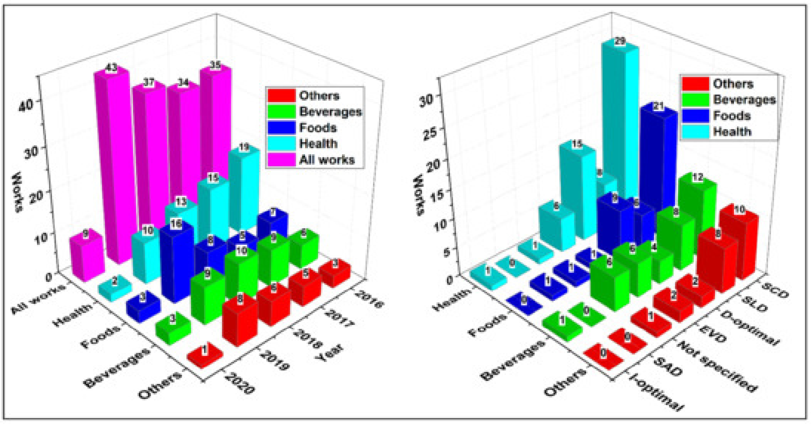

Figure 2. Number of works by areas and year using MDs according to the search from January 2016 to February 2020.

2.3. Application of Mixture Design in Beverage

Table 1 shows some products that used MDs to improve the conditions for processing or formulating beverage products, classified into four subdivisions following careful previous analysis: alcoholic beverage, milk-based beverages, several beverages, and several juices.

Table 1. Application of mixture design in the beverage.

Papers	n_{ref}	References for Data Analysis
Application in Beverage	**37**	**Refs.**
Alcoholic beverage	**1**	[31]
Milk-based beverages	**14**	[32][33][34][35][36][37][38][39][40][41][42][43][44][45]
Several beverages	**9**	[18][46][47][48][49][50][51][52][53]
Several juices	**13**	[17][54][55][56][57][58][59][60][61][62][63][64][65]

In **alcoholic beverages**, simplex-lattice MDs was applied to craft beers to understand the sensory contribution of different hops (Cascade, Chinook, and Centennial) added to the American beer style. The study demonstrated that it is possible to achieve similar aroma profiles when dry-hopping beer with varying blends of Cascade, Chinook, and Centennial hops [31]. The use of MDs for these products has been scarce, demonstrating the possibility for future studies that seek to formulate alcoholic beverages with functional or antioxidant properties, as well as evaluate the effects of additions of spices in a beverage at different stages of fermentation, mixtures of raw materials, formulations of gluten-free or non-alcoholic beverages, among several other possible applications [14].

In **milk-based beverages**, the most frequent applications of MDs aim to improve the rheological, functional, sensory, and antioxidant properties of yogurts and fermented beverages based on milk. Probiotic products were most frequently evaluated, such as yogurt [34][36][37], fermented milk [39], and chocolate beverages [35]. Furthermore, other conventional products, such as yogurt [32][38][43] and dairy drink [45] formulation; yogurt [41] and milk chocolate [33] diet or light; fermented milk [40][44] and soy milk-based beverage [42] have been reported.

In this works, the authors use MDs for formulations of yogurt or fermented milk symbiotics, probiotics, or organic [34][37][39], with various applications. Such as investigate the influence of starter cultures mixtures for product development [36][43], evaluate the effects of different gums and their interactions on rheological, physicochemical, and sensory properties [32][35][40][44], formulate beverages with low/free sugar content [41][42], formulation of drinks with natural sweeteners [33], fortified with antioxidant [38], or for the formulation of low-cost milk drinks obtained from by-products [45].

In **several beverages**, the MDs were used to formulate some unconventional beverages, such as the development of a drink based on sweet potato peels, and a tea based on rooibos (*Aspalathus linearis*), white tea (*Camellia sinensis* var. *sinensis*), and roasted mate (*Ilex paraguariensis*) optimizing the antioxidant and antiproliferative activity of beverages [18][52]. As well as other formulated beverages, such as the development of banana, strawberry, and juçara smoothie [50], carbonated soft drinks formulated based on tagatose, sucrose, and stevia [47][49], coffee [48][51], peanut drink [46], and soursop [53] beverage formulation. Among the applications of MDs in several beverages, we highlight the authors' attempt to achieve improvements in sensory parameters, antioxidant, physical and chemical properties, and rheological of beverages.

In **several juices**, the applications of the MDs were in functional fruit juices [17][55][56][57][58][59][60][62][63][64], powders [54][61], and the quality of sugarcane [65] juice. In addition, the MDs have often been applied in formulations of probiotic and energetic functional juices to improve these products' sensory, antioxidant, and nutritional properties with potential benefits for consumers' health [54][56][60][61].

2.4. Application of Mixture Design in Food

In these subdivisions, several products are reported in which MDs were used for food formulations (**Table 2**). This group was classified as animal origin, bakery product, dairy frozen, fruit jelly, and vegetable origin according to careful analysis.

Table 2. Application of mixture design in food.

Papers	n_{ref}	References for Data Analysis
Application in Food	**39**	**Refs.**
Animal origin	**10**	[19][66][67][68][69][70][71][72][73][74]
Bakery product	**16**	[75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90]
Dairy frozen	**3**	[91][92][93]
Fruit jelly	**5**	[94][95][96][97][98]
Vegetable origin	**5**	[99][100][101][102][103]

In **animal origin** products, MDs have been used to formulate mortadella [68], poultry pâté [69], and beef patties [73] low-fat; sausage [67] and grilled beef [71] with aromatic herbal; sodium-reduced sausages [19][66]; prebiotic sausage formulation [72], gluten-free chicken nugget [70], and honeydew honey [74].

In general, part of the studies have used MDs for formulations of probiotic products of animal origin, such as the formulation of a prebiotic sausage with inulin, konjac, and starch [72] or formulation of a poultry pâté with inulin and lentil flour [69]. Other uses of the MDs were to try to reduce the fat or sodium content in these products. Such as formulating a low-fat mortadella using beef meat, pork meat, and pork back fat [68], formulation of sodium-reduced lean sausages with fish oil seeking partial replacement of NaCl by KCl and sodium tripolyphosphate [19][66], and the formulation of low-fat beef patties with the partial animal fat replacement by cold-pressed grape seed oil and pomegranate seed oil [73].

Other less conventional applications of MDs were for formulations of natural sausages with the addition of aromatic herbs to slow the oxidation of lipids and control the spoilage bacteria in the food [67], or to evaluate the inhibitory effect of spices/herbs and their mixtures on the formation of heterocyclic amines and mutagenic activity of grilled beef by MDs [71]. Moreover, there was only one report for the development of gluten-free industrialized animal products, in which the authors formulated a gluten-free pasta based on three Thai rice flour for use in a frozen battered chicken nugget [70].

In **bakery products**, MDs have been used in functional milk [85], chocolate [82], pecan nut [89][90], and sponge [86] cake formulations; gluten-free formulation of bread [75][81] and cakes [76]; noodle [88] and rice bread [87] formulations; cake [77] and staple bread [83] formulation; cassava crackers enriched [84]; flour [79] and whole-food [78] blend formulation and cereal recipe [80].

Among the most frequent applications of MDs in bakery products are formulations of gluten-free products, such as the formulation of bread using sorghum flour, rice flour, and millet flour [75]; a gluten-free bread based on chickpea flour [81], and a gluten-free cake enriched with protein [76]. Other applications of MDs extend the incorporation of products with different purposes, such as inserting jujube flour in the sponge cake [86], the addition of tikhur starch as a substitute for semolina in the preparation of baked milk cake [85], formulation of chocolate cake with partial replacement of wheat flour with yacon and maca flour [82], formulation of cassava-fish crackers with a combination of ingredients such as cassava starch, high-quality cassava flour, and fish flour [84], formulation of rice noodles that include combinations of gelatinized corn starch, xanthan gum, and guar gum to improve the tensile strength of cooked noodles [88] and the formulation of a low-cost fiber-rich whole food from residues from the processing of orange juice [78].

In **dairy frozen**, the use of MDs was scarce. Among the applications, the use of MDs to optimize the combination of stabilizers (stone gum, carboxymethylcellulose, and guar gum) in the ice cream formulation [93], for the formulation of ice cream mix powder using milk protein, fat, sucrose, stabilizers, emulsifiers, and water [91], and formulation of antioxidants-rich ice cream containing aqueous extract rich in phenolic compounds and potential functional properties made of *Ilex paraguariensis*, *Melissa officinalis*, and *Cymbopogon citratus* [92].

In **fruit jelly,** the MDs were used for functional jelly formulations. Such as the formulation of a jelly enriched with apple puree, concentrated apple juice, and juice from sea-buckthorn berries added during the gelation of jelly [96] or the optimization of native Brazilian fruit jelly with jabuticaba, pitanga, and cambuci based on sensory and nutritional characteristics [94]. Other jelly formulations have been reported, such as jelly with Swazi indigenous fruits tincozi, tineyi, and umfomfo [95], jelly formulation of red fruit with blackberry, blueberry, and strawberry [97], and produce a pestil (fruit leather) from commercial pomegranate juice using xanthan gum, locust bean gum, and pregelatinized starch [98].

In **vegetable origin** products, the use of MDs went to tomato sauce formulated with tomato puree, onion puree, and extra virgin olive oil [103], elaboration of probiotic creamy sauce-based soymilk with okara flour fermented by *Lactobacillus acidophilus* [100]; oxidative stability of soybean oil with natural antioxidant from Tunisian aromatic plants [101][102] and replacement of salt NaCl by KCl and $CaCl_2$ in tomato soup using electronic tongue and mixture design [99].

2.5. Application of Mixture Design in Pharmaceutical Health

According to **Table 3**, the main applications of MDs in pharmaceutical health are for the development of novel products or the formulation of several drugs. This area was subdivided into five classes: drug formulation, encapsulation, extraction compounds, functional activity, and foams/or films-based.

Table 3. Application of mixture design in pharmaceutical health.

Papers	n_{ref}	References for Data Analysis
Application in Pharmaceutical Health	**59**	**Refs.**
Drug formulation	**36**	[15][20][21][104][105][106][107][108][109][110][111][112][113][114][115][116][117][118][119][120][121][122][123][124][125][126][127][128][129][130][131][132][133][134][135][136]
Encapsulation	**6**	[137][138][139][140][141][142]
Extraction compounds	**6**	[143][144][145][146][147][148]
Functional activity	**9**	[149][150][151][152][153][154][155][156][157]
Foams/films-based	**2**	[158][159]

In **drug formulation**, the greatest number of studies using MDs stands out. The application of this method in developing pharmaceutical products has been more explored than in other areas. In this sense, the researchers have used MDs to optimize the composition of formulations and simultaneously estimate the main effects and the interaction of all variables in a drug formulation for several diseases, such as osteoporosis, cardiovascular, cancer, AIDS, dermatological, tuberculosis, gastrointestinal, etc.

The use of MDs has also been explored for the formulation of **encapsulants**. In this step, it is common to mix two or more components to improve specific properties of drugs, and a great way to evaluate the interaction between these encapsulating agents is through MDs. Among some applications, we can list the optimization of the ratio of materials to produce the cinnamon essential oil microcapsules by spray-drying with gum Arabic, maltodextrin, and inulin [137]; or to evaluate the effect of encapsulating agents (gum Arabic, modified starch Capsul™ and maltodextrin DE 5) on anthocyanin retention in microcapsules produced by spray-drying of raw pomegranate juice [138]. In addition, to formulate a bionanocomposites for entrapment of probiotic cells (*Bacillus coagulans*) using bacterial nanocellulose, pectin, and *Schizophyllum commune* [139]; or for the formulation of Turkish oregano extract microcapsules prepared by spray-drying using different concentrations of maltodextrin and gum Arabic as encapsulating agent [140]; or to check the performance of

Zingiber zerumbet oil encapsulation [141]; or encapsulation using carbohydrate, protein, coconut oil mixtures on the viability of probiotic cells (*Lactobacillus bulgaricus*) during spray-drying [142].

The **functional activity** can have several classes, where antioxidant and antimicrobial are the activities most combined with MDs recently. MDs have been used to evaluate the synergistic effects of antioxidant activity on mixtures of the essential oil from *Apium graveolens* L., *Thymus vulgaris* L., *Coriandrum sativum* L., and essential oils from *Ocimum basilicum* L., *Origanum majorana* L., and *Rosmarinus officinalis* L. [150][151][153]. To maximize the antimicrobial activity of essential oils combined against *Escherichia coli* in milk [149] and *Salmonella typhimurium* [152], or to optimize strain mixture of *Lactobacillus* with the highest antimicrobial activity against common food-borne pathogenic bacteria (*Escherichia coli*, *Salmonella enteritidis*, *Listeria monocytogenes*, and *Bacillus cereus*) [154], the nematocidal activity of artemisia extract [155], maqui berry extract as an antioxidant/anti-inflammatory agent [156] and optimization of soy protein isolate, bovine whey protein and egg white protein hydrolysis with the protease Flavourzyme™ 500 L [157].

Certainly, the combination of essential oils generally expresses some interaction effect, and they can be synergistic, antagonistic, additive, or indifferent. In this sense, the MDs use has presented excellent perspectives for future studies to evaluate the effectiveness of several types of functional activities of these products [14].

MDs have been applied to **extract compounds** from various medicinal plants, such as anthocyanins and phenolic compounds from jabuticaba skin and seed, by mixing solvents [143]; to optimize the activity of total phenolic and flavonoids compounds from mixture herbs *Cnestis palala*, *Urceola micrantha*, *Labisia pumila*, and *Microporus xanthopus* [145]; optimize the solvent mixture to extract total phenolic content and antioxidant capacity of camu-camu (*Myrciaria dubia*) seeds [147]; optimize the solvent proportions for extraction of aporphine alkaloids from the leaves of *Unonopsis duckei* [148]; optimize the extraction of curcuminoids from turmeric using ethyl lactate, ethanol, and water under mild conditions [146]; and optimization of essential oil extraction from Pitanga (*Eugenia uniflora* L.) leaves with petroleum ether, *n*-hexane, methanol, and ethanol [144].

In **foams/films-based**, the MDs were used in the formulation of edible films/coatings composite with different proportions of pectin, alginate, and whey protein concentrate for evaluated for physicochemical characteristics on the final product [159] and formulation of foam of cassava starch, peanut skin, and glycerol to improve mechanical flexural mechanical properties and water absorption capacity [158].

2.6. Application of Mixture Design in Other Areas

Table 4 presents a subdivision of the MDs' possible applications that can be used within the area, and these subdivisions were classified as applications related to the area: animal, bioenergy, biology, and materials.

Table4. Application of mixture design in other areas.

Papers	n_{ref}	References for Data Analysis
Application in Other Areas	**23**	**Refs.**
Animal	**3**	[160][161][162]
Bioenergy	**9**	[163][164][165][166][167][168][169][170][171]
Biology	**4**	[1][172][173][174]
Materials	**7**	[22][23][175][176][177][178][179]

According to **Table 4**, MD research in **bioenergy** aims to optimize biodiesel synthesis from a blend of five different oils [169]; investigate the effects of cellulose, xylan, and lignin constituents on biomass pyrolysis characteristics and bio-oil composition [165]; production of biomethane using municipal sludge wastes, grease trap waste, and meat processing waste [167]; investigate the ability of the oleaginous yeast *Debaryomyces etchellsii* strain for lipid production for biodiesel manufacture using different agro-industrial wastewaters (cheese whey, expired soft drinks and fresh olive mill) as substrates [163]; investigate the effect of light wavelength on *Dunaliella salina* to increase microalgae lipid productivity for biodiesel production [164]; optimization of viscosity and density of refined palm oil-Melaleuca Cajuputi oil binary blends for a novel biofuel [168]; formulation of a vermicomposting in organic matters with dairy manure vermicompost, straw, and peat using MDs in cucumber seedling experiment to evaluate the compressed substrates [171]; optimization of concentrations of the solvents ethanol, acetone and water in the extraction of total phenolics present in cashew apple bagasse [166] and optimization of a method for the determination of metals from palm oil by flame atomic absorption spectrometry [170].

For the **materials** area, MDs have been used in glass formulation using iron phosphate base glass system that contained P_2O_5, Fe_2O_3, Al_2O_3, Na_2O, and SO_3 [22]; hydraulic oil formulation with different materials based on specific restrictions applying multiresponse optimization [177]; analysis of the effects of nano-oil additives (using ZnO, Si_3N_4 and carbon nanotubes) on the wear properties of AISI 4140 steel material [178]; formulate and examine the mechanical properties of cotton shell particles integrated into glass-fiber-reinforced polymer composites [175]; optimization of bitumen formulations using asphaltic residue, vacuum residue, and three aromatic extracts (by-products) from the refining process of base oils [176]; formulation of alkali-activated cement mortars incorporating glass powder, slag, and calcium aluminate cement [23]; and investigate the arsenic (V) removal from waters using synthetic minerals using synthetic poorly crystallized aluminum hydroxide, calcined layered double hydroxide, and two-line ferrihydrite [179].

In **biology** applications, MDs propose substitutes of bacteriological agar manufacture in terms of texture by using some reported gelling agents used by food and agroindustry [172], metabolomic fingerprint investigation of reference and crossed coffees [1], secondary metabolites from *Mikania laevigata* leaves [173] and development of a chromatography method to determine drugs of abuse [174].

In the **animal** area, MDs were used for the development of essential oil-based phyto-formulations to control the cattle tick *Rhipicephalus microplus* using a mixture of the cinnamon (*Cinnamomum zeylanicum*), cumin (*Cuminum cyminum*), and allspice (*Pimenta dioica*) [160]; formulation of functional foods for animals mixing complex extracts of *Rhodiola crenulata*, *Astragalus membranaceus*, and *Panax quinquefolius* [161]; and development of an analytical chromatography method for the simultaneous investigation of veterinary drugs in poultry litter [162].

3. Behaviors, Trends, and Perspectives of Mixture Design Applications

Regarding the use of mixture design, the main perspective raised was the development of healthier products, such as the formulation of symbiotic products, which combine probiotics and prebiotics in the form of synergism, and products that aim to reduce the content of sodium, fat, sugar, or gluten from food. Given the greater concern with food quality and improved quality of life, consumers have increasingly chosen these products, which have leveraged and heated the market in this sector. Moreover, there is a growing interest in formulations of free gluten, sugar, or lactose products, especially for celiac, diabetic, and lactose intolerance prevalence.

Another emerging field of research has been studies related to allergenic substances in foods from animal or plant sources that can cause an overreaction of the immune system. In our search, there were no reports about works on this theme. In this sense, MDs' applications can be great tools for future formulations of these types of products.

We also observed promising prospects for studies to evaluate the substitution of chemical additives added to food and pharmaceutical products, such as antioxidants and synthetic stabilizers. Thus, the replacement by natural products such as herbs, fruits, and co-products from industrial processes are great paths to be followed, as they generate products with greater health benefits, add value to co-products, and have been the focus of intense research. Moreover, MDs are promising tools to assess the effects of synergistic interactions of functional activities, such as the antioxidant, antimicrobial and antiviral activity of essential oils and extracts of natural products.

Recently, the science and technology of the production of alcoholic beverages has been taken to another level. Consumers have shown a preference for functionalized drinks, such as the consumption of craft beers, one of the main reasons for this market's leverage [14]. This trend has been growing and opens the possibility of using MDs for formulations of craft beers and other alcoholic beverages.

Though drug formulation has been the main use of MDs, this sector still has an overall capacity for research in nanotechnology, such as the development/formulation of novel NLCs, SMEDDS, SNEOFs, S-SNEOFs, SNELS, microemulsions, nanoemulsions, microencapsulation, nanosuspensions, and nanocrystal-based products.

Trends in the use of MDs in other areas are growing, some promising fields for the application of these tools have been reported, such as the reuse or use of sources from renewable raw materials and industrial waste, formulations of growth media, development of novel analytical methods, nanotechnology, novel materials such as graphene, silicene, perovskite and metal-organic frameworks (MOFs) with specific characteristics for many applications.

Another general trend is the use of MDs to solve problems with multiple responses: restrictions of maximum, minimum, and target values for the responses that can be applied when seeking a formulation [5][6][14]. The strategy most used to optimize multiple responses makes use of the desirability function (D), proposed by Deringer and Suich [180], and other methods such as overlaid contour plots, constrained nonlinear optimization, and a Bayesian approach, which has also been employed [181]. From a practical point of view, multiresponse optimization makes the use of MDs more attractive. Among some promising examples of the application of the desirability function (D) present in the literature, we can mention the multiresponse optimization of the oxidative stability of biodiesel from natural [16] and synthetic [30] antioxidants, or a multiresponse optimization of the efficiency and cost of synthetic antioxidants added to biodiesel [6], or biodiesel formulation [5], or a multiresponse optimization of the effects of adding spices with antioxidant compounds in craft beer [14].

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