TUTORIAL REVIEW

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Combining DoE and MASE: a winning strategy for the isolation of natural bioactive compounds from plant materials

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The successes achieved in pursuing a nature-aided drug discovery (NADD) program are many and well-known, but it is still considered a second-order approach. Biomass extraction is a fundamental and critical step in the NADD process and often requires a high volume of usually organic and not eco-compatible solvents and a prolonged time. Optimization of such procedures could drastically decrease the costs required for the NADD process, also considering waste management. For this reason, many extraction techniques have been developed, among which one of the most diffused is microwave assisted solvent extraction (MASE). The MASE procedure is well suited for use in the drug discovery phase from natural sources. Still, there are several factors to consider, and the one-factor-at-a-time (OFAT) approach risks limiting the advantages the technique provides. The way to make it truly green is to couple MASE with DoE, even if this winning combination is limited. Consistently, we analyze the 10-year literature (2013–2022), reporting a critical discussion about DoE applied to set up MASE protocols for the extraction of metabolites (both performed with traditional solvents and with ionic and eutectic solvents) and essential oils.

Introduction

Natural matrices have always represented an invaluable source of active pharmaceutical ingredients.[1–3] Over the years, different organisms have been considered as starting points of the Nature-Aided Drug Discovery (NADD) process, *e.g.*, plants, lichens, animals, and microorganisms, either terrestrial or marine.[4] The successes achieved pursuing this approach are many and well-known.[5] The wide chemical diversity is the strength of natural products (NPs), which allows molecules to be obtained with various mechanisms of action and, therefore, suitable for various fields of application.

NADD is still considered a second-order approach concerning molecular modeling- and synthesis-driven drug discovery, although only 33.3% of the in-commerce small molecule drugs are fully synthetic compounds.[6] The main reason is the high

time and costs of the extraction and fractionation procedures required to obtain pure active ingredients from a natural matrix. Notably, biomass extraction is a fundamental and critical step in the NADD process and often requires a high volume of usually organic and not eco-compatible solvents, and a prolonged time (from 1 to 5 days).[7,8] Optimization of such procedures could drastically decrease the costs required for the NADD process, also considering waste management. For this reason, many extraction techniques have been developed over the years, moving from conventional (*i.e.*, maceration, percolation, and steam distillation) to the so-called unconventional methods (*i.e.*, ultrasound- and microwave-assisted extraction, supercritical fluid extraction, and pressurized solvent extraction).[9–11]

This review is focused on the Microwave-Assisted Solvent Extraction (MASE) methodology that exploits microwave radiation to heat the natural matrix. Microwaves are part of the electromagnetic spectrum, with frequencies from 300 MHz to 300 GHz corresponding to wavelengths ranging from 1 m to 1 mm.[12] The heating efficiency depends on the dielectric constant and dielectric loss of the molecules irradiated; the former parameter quantifies the molecule's capability to absorb the microwave energy, while the latter defines the molecule's ability to convert radiation energy into heat.[13] The microwaves transfer energy to the molecules by ionic conduc-

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tion and dipole rotation. Free ions or ionic species inside the cell move under the influence of the force of the oscillating electric field of the microwaves; this induced electrophoretic migration causes friction between the charge carriers and the medium, leading to heat production, thus defining heating by ionic conduction. Concurrently, molecules having non-zero permanent electric dipole moments try to align themselves with the direction of the force of the microwave oscillating electric field, colliding one against the other and producing heat (heating by dipole rotation). In conclusion, due to the molecular electrophoretic migration and rotation, the energy delivered by the electromagnetic waves to the molecules is transformed into thermal energy, and an increase in the temperature of the irradiated system occurs. This highly efficient heating system offers several advantages compared to conventional methods.

MASE offers both economical and practical advantages with respect to conventional methodologies, in line with its intrinsic green and eco-sustainable nature, like a shorter extraction time, less use of solvents and the possibility to substitute hazardous ones with more eco-sustainable alternatives, while maintaining comparable or even higher yields. Another important advantage of MASE is related to energy efficiency. Different from microwave-assisted organic synthesis, where it has been shown that energy consumption can be even higher than traditional heating systems (especially when working on a bench scale), a different picture emerges from literature data for MASE.[14] In fact, a recent environmental impact assessment study concluded that MASE shows a better environmental score than conventional techniques and ultrasound assisted extraction, mainly due to the amount and origin of electricity used.

In this work, the authors concluded that its better performance is due to the more efficient extraction with reduced electricity consumption.[15] The different results obtained considering microwave-assisted organic synthesis and MASE can be explained considering that extractions of natural matrices are performed on tens of grams to a kilo scale[16] As stated in the literature, these scales are associated with an improvement in energy efficiency on a kJ mol^{-1} basis.[17] Moreover, also the already cited significant saving of time plays a pivotal role in reducing energy consumption.

Other advantages of MASE are also related to its high reproducibility and robustness.[18] Its high extraction efficiency with solvents such as water and ethanol allows the extraction of non-polar metabolites without the use of other less (or no) eco-friendly solvents and even thermolabile compounds. Today its use on an industrial scale is limited by the high costs associated with the development of *ad hoc* apparatus, even if steps forward have been taken.

More in detail, the efficiency of MASE is related to many operating factors such as the solvent used, and the liquid/solid ratio, the operating temperature and extraction time, the microwave power, and the rate of stirring, as well as some characteristics depending on the sample, like its water content. Considering this large number of variables, optimiz-

ation of the procedure is a critical step. A literature search shows that most published research papers address the optimization of a MASE protocol by following a heuristic approach. Nonsystematic, experience-driven approaches often entail many experiments and do not allow the understanding of the factors' mutual influence. In recent years, Design of Experiment (DoE) is becoming increasingly popular in optimizing the extraction of natural matrices. Therefore, the combination of DoE and MASE may be a winning strategy to set up the extraction of metabolites from natural matrices with a green approach. The DoE approach aims at minimizing the number of experiments required for method/process/product optimization, resulting in saving the amount of solvent, time required, and consequently, energy used. Despite the significant advantages of this combination, DoE is still under-exploited in microwave-assisted extraction method development, as evidenced by the number of papers published (Fig. 1). Still, the number of articles retrieved using both "design of experiments" and "microwave extraction" as keywords on Scopus is very low (a maximum of 37 papers was reached in 2021). In the present paper, after an overview of DoE, we deepened the potential of the combination of these two techniques, reviewing the literature from 2013 to 2022. More in detail, we conducted a bibliographic survey through Scopus and PubMed databases using the keywords "microwave assisted extraction", "MASE", "MAE", "experimental design", "design of experiments", "DoE", "quality by design", and "QbD", together with their possible combinations using the Boolean operators "AND". In addition, we excluded from the survey studies based on heuristic and univariate (OFAT) methodologies and publications that reported extractions with combined techniques, such as combined ultrasound- and microwave-assisted extractions.

This review is proposed to inform the readers about the pros and cons of using DoE for the development and optimization of MASE procedures.
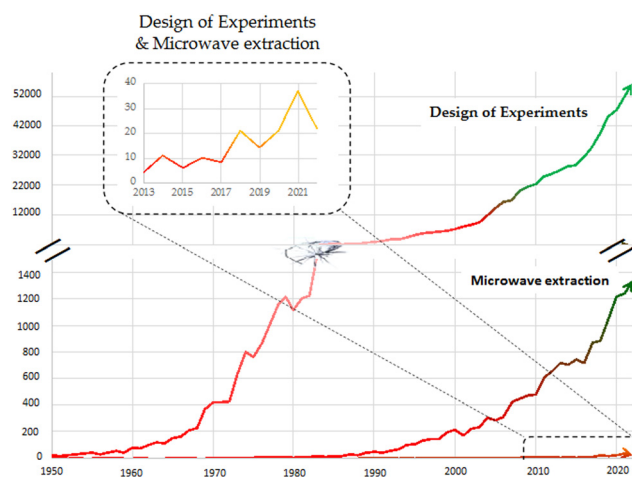

Fig. 1 Number of articles retrieved using keywords "design of experiments" (upper line), microwave extraction (middle line), and both "design of experiments" and "microwave extraction" (lower line). Source: Scopus, updated January 2023.

Design of experiments

Design of experiments (DoE) is a rational approach developed by mathematicians for about one century now that can be applied to any process with measurable inputs and outputs. DoE was initially developed in parallel with statistical methods for improving crop yields in the early 1920s.[19] It rapidly became an essential tool for studying research methodology, quality improvement, and statistical process control, in several fields of application, like agriculture and botany, psychology, engineering, industrial chemical processes, and many other applied sciences.[20]

The strength of DoE is that it is the most efficient, cost-effective approach to collect information about the best quality (expressed by the experimental variance of the output data), studying virtually any number of factors and requiring the least number of experiments compared to any other approach. Based on mathematical evidence, DoE is superior to heuristic or one-factor-at-a-time (OFAT) approaches in terms of efficiency (expressed by the ratio of the amount of information collected to the number of experiments performed).[21] Although this is a long-established fact for mathematicians, the same cannot be said for experimenters in applied sciences. The OFAT method is still widely used in applied experimental research because it requires no specific training and is perceived as "rigorous".

Out of the many advantages of DoE, it is the only approach that provides knowledge regarding the relevance of the single factors and their interactions, whereas the OFAT approach cannot investigate interactions.[22,23]

The present trend favoring the diffusion of DoE is related to the availability of powerful computers and information technology tools (*e.g.*, open source software), that allow learning the use of DoE by applying it as a procedure, following a few simple steps.[24] The Japanese engineer and statistician Genichi Taguchi first elaborated on this way of proposing DoE to potential users,[25] differently to the Western more formal statistical training offered in academia.[21,26,27] In the following, we summarize the rational procedure revisited by European research groups for teaching DoE to non-mathematicians.[28]

The definition of the experimental response, which must be numeric, is the first step in the process. Accordingly, describing the system and analyzing the technical details related to the response measurement is the procedure's fundamental and more difficult phase. Then, a list of all the factors influencing the experimental response and their levels of variation is created. The variation intervals of factors define the space to study the response (design space).[28,29] Once these steps are completed, the focus moves to model selection and data interpretation. Two types of experimental designs are available: screening and optimization designs. The first ones are usually used to study the effect of single factors and their two-term interactions on the response. The latter ones are instead used to make predictions (on maxima, minima, or other critical points of the response function) and fully describe the process under examination.

The following list of techniques available in DoE is far from complete since the present section aims to introduce the reader to the topic, showing the main tools available to practitioners. Screening designs include full factorial, fractional factorial, and Plackett–Burman designs.[30] Taguchi designs are used to reduce the noise, select the more relevant factors, and optimize the settings of a process.[31] Definitive screening designs allow studying single factors, their interactions, and quadratic terms when many factors are involved (*i.e.*, more than 6).[32] Response surface designs (RSM), including central composite, Box–Behnken, and Doehlert,[33] are canonical quadratic designs used to describe the system fully. The RSM designs are of practical use for a small number of factors (<5) because they involve quadratic polynomials with many terms. In addition to these so-called "canonical" or "optimal" designs, researchers may use D-optimal designs when the system involves both continuous and non-numerical factors varying over more than two levels.[34] Mixture designs are instead the designs of choice when dealing with non-independent and constrained numerical factors.[35,36]

Generally, the first-choice models are two-level full factorials (where the number of experiments is 2^k, with k being the number of factors) or fractional factorials (number of experiments 2^{k-p}, where k is the number of factors and p is the size of the fraction).

On the other hand, using the RSM, quadratic models are introduced to describe the response as a function of factors as accurately as possible.[37] These designs describe the response dependence on the experimental factors and predict the response values over the entire domain of factor variation.[38] Different designs belong to this second group, like (i) central composite designs, which contain a factorial or fractional factorial design with central and other additional points that allows calculating the response surface, (ii) Box–Behnken designs, which is a class of second-order designs based on a three-level incomplete factorial design, and (iii) Doehlert designs, which are obtained from regular k-dimensional simplexes (regular geometric figures with $k + 1$ vertices) of which the simplest, in 2 dimensions, is the equilateral triangle.[39]

Once the experimental design is selected, this is one-to-one related to the model equation and matrix (Fig. 2). A simpler
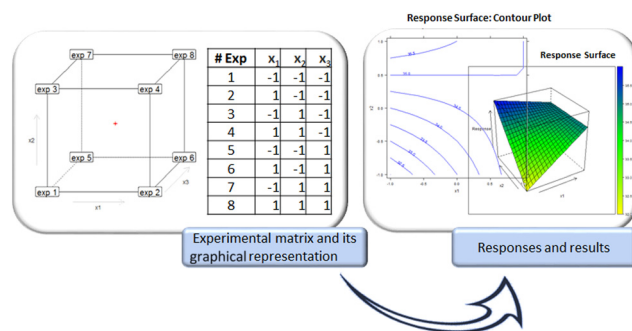

Fig. 2 Different steps characterizing the DoE approach. The example refers to a full factorial design.

experimental matrix is deducible based on the model matrix, and the experimental plan is obtained accordingly. The experimental plan is a table that presents the actual values of the factors for each experiment. The experiments are performed in random order following the fundamental recommendation given since the birth of DoE to obtain a fair estimate of the model coefficients. Regarding the in-depth description of specific experimental designs, models, and details concerning the statistics involved in using these tools, interested readers are referred to the fundamental literature on the subject.[5–21,27]

The last part of the experimental design involves transforming the data obtained into information and their analysis. The model must be examined to determine if it shows good predictability; this means that it must adequately represent the response function in the experimental domain. In other words, the model is judged adequate if the value of the calculated response for every point of the domain matches the value obtained from the outcome of experiments carried out independently from those used to build the model itself.

Design of experiments approach to set up MASE protocols

In this section, articles in which DoE has been applied to set up an appropriate MASE methodology are presented and critically evaluated, dividing them into three groups: the first group includes studies on extraction of metabolites, the second on essential oil extraction, and the third focuses on extraction performed with ionic or eutectic solvents. For the sake of clarity, the main factors affecting the efficiency of microwave extraction are briefly discussed first.

Factors affecting microwave extraction efficiency

Solvent. The choice of an appropriate solvent plays a very important role in any kind of extraction technique. Particularly, in MASE protocols the solvent must be selected based on its ability to absorb the microwave radiation and convert it into heat.

Solvents are classified into low, medium, or high absorbance based on the ability to absorb microwaves. Typical low-absorbance solvents are hexane, toluene, ethyl acetate, and diethyl ether. Water, dimethylformamide, and acetic acid are classified as medium absorbance solvents, whereas ethanol, methanol, formic acid, and ethylene glycol are high-absorbance solvents.

Moreover, growing interest in eco-friendly solvents like ionic liquids and deep eutectic solvents is developing.

Finally, Solvent-Free Microwave Extraction (SFME) is also possible. The water inside the cells absorbs the microwaves, causing heating of the system and, consequently, the rupture of cell walls. This technique is primarily used to extract essential oils or other volatile compounds.[40] Unlike the so-called process parameters (*e.g.*, liquid/solid ratio, extraction time, microwave power, temperature, water content and other quantifiable characteristics), which can take numerical values and

are often continuous variables, some factors, like pure solvents, may not be numerical variables. Factors representing the type of solvent used for extraction, for example, "ethanol", "acetone", or "water" are qualitative variables. However, the levels of qualitative variables must be referred to as numerical quantities. Therefore, if the choice is between two solvents (*e.g.*, ethanol or water), the selection of the solvent type is usually coded with "−1" indicating the choice of solvent "A" (*e.g.*, ethanol) and "+1" indicating the choice of solvent B (in this case, water) in a specific column of the experimental matrix named, *e.g.*, "solvent". If the solvents studied are more than two, the simplest approach is to code the levels using a binary coding, with "1" indicating the choice of the given solvent, as shown in Table 1 for three solvents.

In Table 1, coding 1 indicates the presence of the type of solvent selected, whereas 0 indicates the absence of the solvent. Therefore, experiment#1 uses 100% ethanol, experiment#2 uses 100% acetone, and experiment#3 uses 100% water. The third column is not necessary since it is given by the values of the first two columns.

The same procedure can be applied for any number of solvents, k, bearing in mind that the number of rows in the experimental matrix will be equal to the number of solvents under investigation, but the number of columns is equal to $k − 1$ since the last column is implicitly indicating the choice of the k-th solvent. In Table 1, when both ethanol and acetone are at their 0 levels (*i.e.*, not used), it indicates consequently that water is used as the extraction solvent. An example of this kind of coding can be found in reference,[41] where the influence of solvents as acetone, ethyl acetate or ethanol in the extraction process is investigated by exploiting a DoE model. The fully coded data of the work taken as an example are reported in Table 2.

Liquid/solid ratio. The solvent volume must be enough to cover the sample during the entire process, when the swelling of the matrix occurs. At the same time, the solvent volume should also be selected considering how to optimize the energy delivered to the sample and minimize the process time. A larger volume of solvent may lead to a non-uniform distribution of the heat caused by microwaves, reducing the final yield of the extraction.

Extraction time. Generally, the yield is directly proportional to the extraction time. Still, overexposure to radiation can cause, even at low temperatures and power, the degradation of thermal or oxygen-labile compounds, decreasing the final yield. For this reason, the appropriate time varies from a few to 30 minutes, except for the extraction of essential oils per-

Table 1 Binary coding for the qualitative factor "solvent" studied at three levels, ethanol, acetone, or water

Experiment #	Ethanol	Acetone	Water
1	1	0	0
2	0	1	0
3	0	0	1

Table 2 Examples of coding in one full factorial design with 3 factors, out of which X_1 is qualitative at three levels (solvent, at levels 1, 2, and 3, *e.g.*, Solv1 being acetone, Solv2 ethyl acetate, and Solv3 ethanol), whereas X_2 and X_3 are numerical at two levels (X_2, cycles is numerical non continuous, and X_3, the temperature, is numerical continuous)

Exp #	X_1: Solv1	X_1: Solv2	X_2: Cycles	X_3: T
1	1	0	−1	−1
2	1	0	1	−1
3	1	0	−1	1
4	1	0	1	1
5	0	1	−1	−1
6	0	1	1	−1
7	0	1	−1	1
8	0	1	1	1
9	0	0	−1	−1
10	0	0	1	−1
11	0	0	−1	1
12	0	0	1	1

formed by exploiting a solvent-free procedure, which may require more than one hour.[42,43] A more complete discussion about this topic will be done in the paragraph dedicated to essential oils.

Discontinuous procedures may be applied to avoid labile compounds' yield losses or degradation when a longer extraction time is more desirable. Such procedures apply more than one cycle of microwave irradiation in consecutive steps using a fresh aliquot of solvent every time.

Microwave power. This factor is closely related to the temperature control in the extraction vessel. In microwave-assisted extraction of plant materials, in particular, the destruction of the plant tissue cell walls and membranes leads to the release of the actives into the solvent. The release is therefore driven by the energy provided to the sample by electromagnetic waves. Higher microwave power causes the heating of the sample, increasing the system's temperature.

Generally, higher power determines higher yields and shorter extraction times. However, increasing the power beyond the optimum can lead to the decomposition of labile molecules. Therefore, the microwave power is set considering the target compounds' thermal stability, sample amount, type, the volume of the solvent used, and extraction time.[18]

Temperature. Higher temperature lowers the solvent's viscosity and surface tension, improves the solvent's ability to penetrate the matrix, and increases the solubility of the compounds. The stability of the actives, the microwave system used, and the yield pursued must also be considered during the definition of the extraction temperature.[44] An important issue related to this factor is that microwave dielectric heating is often non-uniform if a sufficient mass transfer cannot be ensured. Moreover, another concern is that most published experiments estimate the temperature by using external IR sensors, which are far less accurate if compared to internal probes.[45]

Water content and other sample characteristics. In the MASE procedure, the effect of the moisture content of materials on heating is crucial, being a parameter directly linked to the dielectric constant.[46]

Microwaves cause the evaporation of the water contained in the sample, developing great pressure inside the cell that promotes its rupture. Moisture also facilitates the transmission of heat through the material.

Moreover, the production of steam in the sample vessel rapidly leads to a build-up of pressure inside the oven that can cause trouble in extraction control. On the other hand, the steam produced and kept under pressure in the sample can facilitate the cells' rupture.[47]

Stirring. Stirring promotes the desorption and dissolution of the target compounds into the solvent since it affects the mass transfer process. Moreover, sample agitation can also minimize the mass transfer barrier created by the concentrated compounds in a localized region due to insufficient solvent, resulting in better extraction yield.

All these factors, except for stirring, have been considered in the three groups of articles considered, even with some differences. Thus, except for the extraction time, all the other factors have been differently considered, *e.g.*, the solvent seems more influential in general solvent extraction, power and liquid-to-solid ratio in essential oils, and temperature in ionic/eutectic solvents (Fig. 3).

Microwave assisted solvent extraction of metabolites

In most cases, microwave assisted extraction is exploited to set up or optimize the extraction of metabolites or a class of metabolites from different natural matrices. Examples in this field are many and can be divided into two main groups: extraction performed with traditional solvents and extraction performed with ionic and eutectic solvents. The strategy and the niceties as the basis of these two groups are different, and they will be discussed separately.
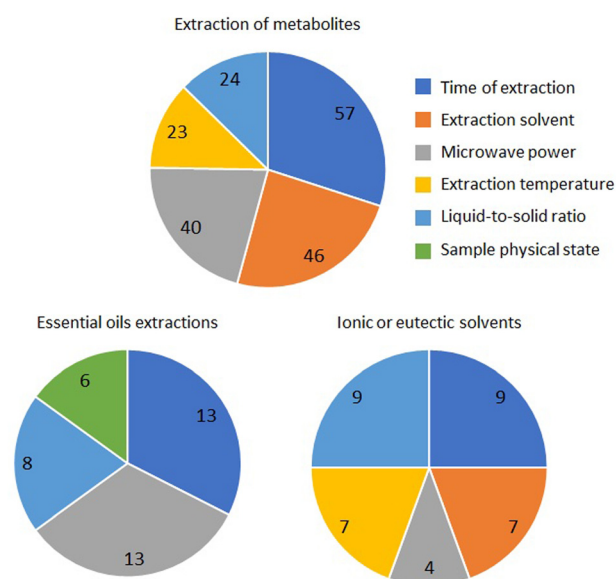
Fig. 3 Recurrence of the factors evaluated in the MASE studies reviewed.

Green Chemistry

Tutorial Review

General microwave assisted solvent extraction of metabolites. In this section, 63 articles have been analyzed, considering different biomasses. Most of them originate from terrestrial plants, but also lichens (entry #18), fungi (entry #36), and marine organisms (entry #50) are represented. A widespread application of DoE and MASE regards processing wastes and byproducts (13 papers, 20%, entries #2, 10, 15, 16, 20, 22, 27, 31, 44, 51, 55, 57, and 60). In about half of the selected articles (63 in total) a preliminary screening of the above-mentioned factors was carried out (29 articles, 46%). This first step aims to select the factors that influence the response or evaluate the ranges of the selected parameters. In almost all papers, the preliminary screening is performed following an OFAT approach, and only a few studies applied an experimental design. Among them, in one case a 12-run Plackett–Burman design (PBD) was used to select the factors significantly affecting the response.[48] The authors obtained evidence that allowed them to decrease the number of factors from five to three and to define their range. In another case study, two different sets of experiments were performed before setting the factors for the final optimization. These sets were performed following full factorial designs and considering different factors (solvent in the first set and power and time in the second).[49]

Regarding the responses, 22 papers over 63 focused on the total phenol yield, followed by the total extraction yield (14 papers), pure metabolite yield (12 papers), total flavonoids and anthocyanins (8 papers each), while other works report on different classes. Of note, some papers don't focus only on the extraction of a metabolite or a class of metabolites, but also on maximizing the activity of the extract. This is the case of works focusing on the extraction of metabolites with antioxidant, antimicrobial and aldose reductase activity. Table 3 summarizes the responses and measurement methods evaluated to describe MASE results in plant material extractions. In such articles, the authors claimed that DoE was helpful in attaining greener procedures as compared with the original ones, such as in entries #1, 2, 5, and 7 just to cite a few. Thus, optimized procedures usually exploited green solvents like water or ethanol and allowed decreasing time and solvent consumption. Furthermore, a recent work estimated that MASE consumed 59% less energy (expressed in kilowatt-hour per gram of total triterpenoids) than maceration.[50]

The most exploited RSM model was the Box–Behnken design (BBD, 30 articles, 48%), followed by the central composite design (CCD, 21 articles, 33%). The success of these two models lies in the fact that they highlight the interactions between parameters and require a limited number of experi-

Table 3 Responses and measurement methods evaluated for describing MASE results and related number of citing articles among the ones considered in the section on plant material extractions

Responses	Measurement methods	Citing articles	Ref.
Total yield	Dry extract/dry matrix × 100	13	41, 53 and 61–71
	UV method	1	72
Total phenols	Folin–Ciocalteau method	21	48, 49, 51–53, 56, 57, 60, 67, 69, 70 and 73–81
	UV method	1	82
Total flavonoids	Aluminum chloride colorimetric modified method aluminum nitrate colorimetric method.	5	48, 51, 69, 74 and 83
	UV method	1	54
		2	55 and 82
Condensed tannins	BuOH/HCl method	1	60
Total tannins	Casein precipitation method	1	74
	Folin–Denis method	1	48
Total saponins	Isolation and weighing	1	84
Total pectins	Isolation and weighing	4	85–88
Total pectins, esterification degree, equivalent weight, anhydrouronic acid and methoxyl content	Isolation, weighing, and titration	1	89
Triterpenoid content	HPLC-UV	1	50
Total anthocyanins	HPLC-UV	1	73
	UHPLC-UV	1	75
	pH differential method	3	49, 66 and 90
	UV method	2	59 and 91
	Association of Analytical Communities official method 2005.02	1	92
Total polysaccharides	Isolation and weighing	2	93 and 94
	Sulphated polysaccharides	1	95
Single metabolites	HPLC	10	41, 49, 58 and 96–102
	HPTLC	2	103 and 104
Alkaloids	HPLC	5	76, 91, 105–107
Antioxidant activity of the extract	ABTS + FRAP + DPPH	3	48, 53 and 76
	DPPH	4	63, 67, 82 and 92
	FRAP + DPPH	1	78
	Not specified	1	59
Antibacterial compounds	antibacterial diameter (mm)	1	108
Aldose reductase	Enzymatic assay	1	63

ments. The other experimental designs that emerged during the literature survey are two-level factorial design,[51] Taguchi design,[52] incomplete 3^3 factorial design,[53] orthogonal array,[54,55] 3-level design,[56] D-optimal,[57] full factorial design,[41,58] randomized block design,[59] and face-centered central composite design.[60,61] All these models emerged a maximum of three times each during the investigations (Table 4).

Going into detail about the factors considered in the DoE, the authors did not always choose the same ones (Table 5). The variability may be due to the natural matrix and the metabolite (or class of metabolites), but it also reflects the different goals of the researchers. Thus, the selection of the factors is related to the desired outcomes, as witnessed in entries #16 and 17. In these cases, the starting biomass is the same (peels of *Citrus sinensis*), while the responses are different (pure metabolite #16 and class of metabolites, pectin, #17), and the range of the considered factors is entirely different.

It is well known that the extraction time plays a relevant role in extraction efficiency. Only six studies indeed maintain a constant extraction time (9%, entries # 2, 3, 6, 8, 9, and 53). In all the examined papers, the extraction time has been considered and it never exceeded one hour and was often ≤5 minutes (25 times, 40%). The short time required for the metabolite extraction represents one of the major advantages of MASE, since the classical approaches often require at least one day of extraction.

The second most frequently recurring factor (40 mentions out of 63 articles, 63%), as it is closely related to the MASE technique, is microwave power. It strongly depends on the characteristics of the oven and is related to the temperature in the sample vessel. Therefore, varying the microwave power means varying the temperature. For this reason, most researchers vary only one of the two factors while holding the other constant. In line with this consideration, in 35 (56%) articles the microwave power is varied, in 18 (29%) the temperature, and only in 5 (8%, entries #2, 12, 13, 22, 58) are both studied. The remaining articles do not consider either factor. In detail, most researchers judged temperature as a factor of interest, claiming that it significantly influences the extraction yield (*i.e.*, entries # 6, 19, and 35). In general, microwave power is more studied than temperature, suggesting a more relevant role in extraction efficiency.

As is always the case in extraction processes from natural matrices, an important factor that must be considered is the extraction solvent. The most used solvents are EtOH (alone or mixed with water, 35 papers, 56%), water (16 papers, 25%) and MeOH (9 papers, 15%). Only three papers report the use of different solvents: ACN (entry #44), MeOH/DCM (entry #45) and ACN/MeOH (entry #61). The limited types of solvents considered highlighted that not all the solvents are suitable for microwave extraction, since not all the solvents are able to absorb microwaves. Moreover, the prevalence of EtOH and water highlights the intrinsic green nature of MASE. Thus, EtOH was also the best choice compared to others (entries #

18 and 30), and, together with water, it is considered a highly eco-sustainable solvent. Also, investigating the best L/S ratio allows for avoiding solvent excess (the best parameter settings often being in the middle of the considered range).[85,96]

Extraction with ionic and eutectic solvents

Ionic liquids (ILs) and deep eutectic solvents (DESs) are classes of solvents that have recently attracted increasing interest as MASE solvents.

DESs were proposed at the beginning of the century as an alternative to ILs to overcome critical drawbacks such as their toxicity, number of synthetic steps, waste products, the fact that they become persistent pollutants in water, and overall cost.

Some authors consider DESs a subclass of ILs, and sometimes they consider these terms interchangeable. On the other hand, other authors underline that despite many similarities, ILs and DESs are different groups of substances. Briefly, ILs are a combination of heterocyclic cations and organic or inorganic anions, whereas DESs are obtained by hydrogen bonding of two molecules, among which one is a hydrogen bond acceptor (HBA) and the second is a hydrogen bond donor (HBD).[109]

DESs can be classified as type I (which combines metal chloride and quaternary ammonium salt), type II (which combines metal chloride hydrate and quaternary ammonium salt), type III (which combines a H-bond donor typically carboxylic acid, amide or polyol with quaternary ammonium salt), type IV (which combines metal chloride hydrate and a H-bond donor), and type V (which combines nonionic molecular H-bond acceptors and H-bond donors).[110]

When the composition of a DES includes chemicals of natural origin, it is defined as a natural deep eutectic solvent (NADES). NADESs are interesting solvents due to their better biodegradability, lower toxicity, and higher solubility properties compared to the organic solvents usually exploited for extracting natural matrices.[111,112] A recent review defines NADES as "one of the most promising discoveries in the field of green chemistry", even though high commercial costs of these solvents still limit their use.[113]

We refer the readers interested in classifying these peculiar substances to the recent comprehensive review of Justyna Płotka-Wasylka *et al.* (2020).[109]

It is impossible to generalize the physical properties of ILs and DESs because of the wide variety of substances that can be obtained by combining the precursors mentioned above. However, some general features are common to all these substances. ILs and DESs have high polarity, low melting points (broadly speaking <100 °C), low vapor pressure, and wide liquid range. They have high density and viscosity, strongly dependent on the temperature. DESs' viscosity can be reduced by adding water to their solutions. ILs and DESs are all highly tunable solvents. Due to their tunable polarity, ILs, DESs, and especially NADES, can dissolve and even stabilize a variety of analytes, including macromolecules such as enzymes.[114,115]

Table 4 Synoptic table of the references reporting the application of DoE to general MASE of metabolites

#	Plant	DoE model	Factors					Ref.
			Time (min)	Power (W)	Solvent	L/S ratio	Temp. °C	
1	*Acacia mearnsii* De Wild. (bark)	FCCD	1–5	150–350	20%–80% MeOH	20:1 (fix)	—	60
2	*Acanthopanax senticosus* (Rupr. et Maxim) Harms (stems)	BBD	15 (fix)	450–600	H$_2$O + 0.8% surfactant	30:1–50:1	50–70	96
3	*Allium cepa* L. (bulbs)	BBD	5 (fix)	1800 (fix)	50%–100% MeOH, pH 2–7	50:1–100:1	50–100 °C	73
4	*Amomum tsao-ko* Crevost et Lemaire (fruits)	BBD	30–75	—	20%–80% EtOH	10:1–25:1	35–65	108
5	*Argania spinosa* (L.) Skeels (hulls)	CCD	15–35	400–800	10%–30% EtOH	—	—	74
6	*Aristotelia chilensis* (Mol.) Stuntz	BBD	2 (fix)	800 (fix)	25%–75% MeOH, pH 2–7	20:1–40:1	50–100	75
7	*Artocarpus heterophyllus* Lamk (wood)	FCCD	10–50	400–800	Aquadest	25:1–1:12	—	61
8	*Berberis asiatica* Roxb. (leaves)	BBD	5 (fix)	100–500	30%–80% MeOH	15:1–45:1	—	48
9	*Berberis* sp. pl. (roots)	CCD	2 (fix)	200–600	40%–100% MeOH, pH 2–5	30:1–70:1	—	76
10	*Carica papaya* L. (peel)	BBD	0.3–3	320–640	H$_2$O, pH 1–3	5:1–25:1	—	85
11	*Centella asiatica* (L.) Urban (tetraploid)	CCD	5–10	100–200	40%– 80% EtOH	10:1 (fix)	—	50
12	*Chromolaena odorata* (L.) King & Rob. (leaves)	Two-level factorial design	1–5	400–800	20%–60% EtOH	8:1–14:1	60–80	51
13	*Chuanminshen violaceum* Sheh et Shan (rhizomes)	BBD	1–15	400–600	H$_2$O	20:1–40:1	50–70	93
14	*Cinnamomum burmannii* (Nees & T.Nees) Blume (bark)	CCD	10–30	120 (fix)	80%–90% EtOH	10:1–30:1	—	65
15	*Citrullus lanatus* (fruit)	BBD	1–3	160–480	H$_2$O pH 1–2	10:1–30:1	—	86
16	*Citrus sinensis* (L.) Osbeck (peels)	BBD	3–20	100–850	—	5:1–25:1	—	97
17	*Citrus sinensis* (L.) Osbeck (peels)	BBD	1–3	160–480	H$_2$O pH 1–2	10:1–30:1	—	77
18	*Cladonia foliacea* (Whole lichen)	FFD	10–15	100 (fix)	Acetone–AcOEt–EtOH	20:1 (fix)	60–80	41
19	*Clitoria ternatea* L. (flowers)	CCD	15–25	—	95% EtOH (fix)	15:1–25:1	40–60	66
20	*Coffea arabica* L. (spent grounds)	CCD	3–6	60–120	50%–99% EtOH	5:1–20:1	75 °C (fix)	67
21	*Coffea liberica* L (seeds)	Taguchi design	5–10	—	60%–80% EtOH	2.5:1–7.5:1	50–90	52
22	*Cola nitida* Schott & Endl. (pod)	BBD	2–10	400–500	EtOH (fix)	100:1 (fix)	55–65	68
23	*Coptis chinensis* Franch. (rhizomes)	CCD	3–7	120–240	25%–75% EtOH	2.5:1 (fix)	—	91
24	*Cordyceps militaris* L. (fruits)	BBD	2–6	300–700	H$_2$O (fix)	20:1–50:1	—	98
25	*Cucumis melo* L. (fruits)	BBD	1–3	300–700	H$_2$O pH 1.5–3	20:1–30:1	—	87
26	*Docynia indica* (Wall.) Decne. (fruits)	CCD	15–45	240–560	40%–80% EtOH, pH 2–6	5:1 (fix)	50–70	69
27	*Eucalyptus globulus* Labill. (wood)	Incomplete 3³factorial design	5–15	150 (fix)	EtOH (fix)	5:1–10:1	50–70	53
28	*Ficus racemosa* L. (leaves)	BBD	2–6	420–490	MeOH (fix)	10:1–30:1	—	103
29	*Fragaria ananassa* Duchesne (leaves)	BBD	20–40 s	300–500	40%–60% EtOH	50:1–70:1	—	78
30	*Glycyrrhiza glabra* L. (roots)	CCD	2–6	—	80% EtOH–80% MeOH–H$_2$O	10:1–25:1	—	70
31	Grape juice wastes	BBD	1–5	100–600	H$_2$O	10:1–50:1	—	90
32	*Hibiscus sabdariffa* L. (calyxes)	RBD	1–9	100–400	50%–80% EtOH	10:1 (fix)	—	59
33	*Hylocereus polyrhizus* Britt. & Rose (peels)	Second order CCD	20–80 s	300–800	H$_2$O, pH 1–3	30:1–110:1	—	88
34	*Inula helenium* L. (roots)	Orthogonal array	3.5–4.5	—	40%–60% EtOH	12:1–18:1	55–65	54
35	*Juglans regia* L. (fruits & seeds)	CCD	6–30 (1–3 cycles)	500 (fix)	50% EtOH (fix)	7.5:1 (fix)	60–100	79
36	*Lachnum singerianum* YM296 (mycelium)	BBD	1.5–2.5	—	NaOH 0.5–1.5M	10:1–20:1	—	72
37	*Mangifera indica* L. (peel)	BBD	5–8	400–800	H$_2$O, pH 1–3	20:1 (fix)	—	89
38	*Marrubium vulgare* L. (aerial parts)	CCD	5–15	100 (fix)	20%–80% EtOH	3:1 (fix)	40–120	71
39	*Morus alba* L. (fruits)	BBD	5–9	150–270	20%–60% EtOH	20:1 (fix)	—	62
40	*Morus alba* L. (leaves)	2-Factor, 3-level design	7–13	480–800	H$_2$O (fix)	80:1 (fix)	—	99
41	*Myrmecodia pendens* Merr. & Perry (tubers)	CCD	3–10	10–50%	0%–80% EtOH	8:1–12:1	—	92
42	*Nelumbo nucifera* Gaertn (plumule)	CCD	2.9–5.3	141–260	36%–84% MeOH	20:1 (fix)	—	105
43	*Nigella glandulifera* Freyn (seeds)	BBD	25–35	350 (fix)	60%–80% EtOH	15:1–25:1	60–80	63
44	*Olea europaea* L. (leaf)	CCD	0.5–1.5	150–250	30% ACN	10:1–20:1	—	82

Table 4 (Contd.)

#	Plant	DoE model	Factors					Ref.
			Time (min)	Power (W)	Solvent	L/S ratio	Temp. °C	
45	*Pachyrhizus* sp.pl. (seeds)	CCD	3–11	—	12%–50% MeOH in DCM	40:1 (fix)	39–71	100
46	*Peganum harmala* L. (seeds)	BBD	8–12	600 (fix)	65%–95% EtOH	20:1–40:1	60–100	106
47	*Phyllostachys edulis* Houz. (leaves)	Orthogonal array	6–8	—	60%–80% EtOH	20:1–33:1	—	55
48	*Phyllostachys pubescens* (bamboo shoots)	CCD	3–5	35 W (fix)	MeOH (fix)	6.25:1–10:1	75–95	80
49	*Physalis alkekengi* L. (calyxes + fruits)	BBD	20–30	250–350	80% EtOH	20:1–20:40	—	84
50	*Porphyra dentata* Kjellman (alga)	3-Level, 4-parameter design	1–5	200–400	10%–90% EtOH, pH 4–10	—	—	95
51	*Quercus cerris* L. (bark)	D-optimal	10–30	200–1000	70% EtOH (fix)	20:1 (fix)	—	57
52	*Rheum australe* Don. (rhizomes)	BBD	5–10	245–490	NaOH 0.01–0.5 M	15:1–25:1	50–70	101
53	*Sedum aizoon* (leaves)	BBD	20 (fix)	—	70%–90% EtOH	15:1–25:1	25–75	83
54	*Selenicereus undatus* (Haw.) D.R.Hunt & *Selenicereus megalanthus* (K.Schum. ex Vaupel) Moran (fruits)	BBD	5–65	600 (fix)	H$_2$O (fix)	50:1–150:1	25–75	64
55	*Spinacia oleracea* L. (general waste)	2-Factor, 3-level design	5–15	—	0%–60% EtOH + HCl	—	60–120	56
56	*Stephania sinica* Diels (whole plant)	BBD	0.5–1.5	150 (fix)	30%–90% EtOH	10:1–30:1	60 (fix)	107
57	*Syzygium nervosum* A. Cunn. (seeds)	BBD	3–4	400–500	40%–60% EtOH	—	30 (fix)	81
58	*Tarchonanthus camphoratus* L. (stems)	BBD	35–55	100–300	MeOH (fix)	—	40–60	104
59	*Vaccinium corymbosum* L. (fruit)	CCD	4–24	71.05–142.1	30% EtOH, citric acid 1.5 M	160:1 (fix)	—	49
60	*Vitis vinifera* L. (lees)	BBD	25–44	50–60	0–100% EtOH	55:1–60:1	85 °C (fix)	57
61	*Zea mays* L. & *Triticum* L. (seeds)	FFD	5–10	—	MeOH–ACN (alone or 1:1)	4:1 (fix)	40–80	58
62	*Zingiber officinale* Rosc. (rhizomes)	BBD	0.3–0.5	400–600	70%–90% EtOH	20:1–30:1	—	102
63	*Zizyphus lotus* L. (Pulp and Peel)	CCD	20–40	200–600	H$_2$O (fix)	20:1–40:1	—	94

Table 5 Responses and measurement methods evaluated for describing MASE results and related number of citing articles among the ones considered in the section of extractions assisted by ionic and eutectic solvents

Responses	Measurement methods	Citing articles	Ref.
Total phenols	Folin Ciocalteau method	1	116
	HPLC	6	117–122
	UV	1	123
Total anthocyanins	pH differential method	1	123
Antioxidant activity	FRAP	1	116
	DPPH	1	123
Single metabolites	HPLC	2	124 and 125

In the context of the present review, ILs and DESs since 2013 have been used for MASE with DoE in only ten studies. Table 5 summarizes responses and measurement methods evaluated for describing MASE results. As found in the review of reports regarding general solvent extraction, the most studied response is the total phenol yield. Other responses evaluated include pure metabolite yield, antioxidant activity, and total anthocyanin content.

ILs and DESs are solvents invented to be task-specific, therefore they are selected carefully before performing analyte extractions. In 6 cases (60%), the HBA choline chloride (ChCl) in combination with different HBDs were indicated as the optimal NADES for MASE (entries #64, 65, 66, 67, 70, and 72).

The percentage of water in the mixture prepared for MASE was demonstrated to strongly influence the results, as it affects the heating rate and facilitates the transport of the analytes from the matrix to the extraction solvent. Three reports describe studies on the percentage of water before selecting the extractive solvent (entries #64, 65, and 68).

Regarding the other process factors (see section "Factors affecting microwave extraction efficiency"), time is the most considered factor. Of note, the ranges of time, L/S ratio and temperature studied do not vary significantly among the different experiments.

Conversely, in the reviewed studies both microwave power and temperature varied over different ranges. In 3 papers, the authors varied power (30%), in 6 (60%) temperatures and only in 1 both (10%, entry #67). Temperature plays a more critical role in extractions with ILs and DESs than microwave power. This trend can be explained by considering that higher temperatures are associated with lower viscosity of solvents, resulting in improved diffusion and analyte solubility. However, operating at too high temperatures can cause solvent degradation.[126] This significant influence of temperature on the results may explain why more attention is paid to temperature than power in this category of extractions. Table 6 lists all the articles reviewed in this section.

Essential oil extraction

The extraction of essential oils (EOs) assisted by microwaves is considered an emergent new method that may substitute tra-

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Table 6 Synoptic table of the references reviewed related to DoE applied to ILMAE and NADES-MAE

| # | Plant | DoE model | Factors | | | | | Ref. |
			Time (min)	Power (W)	Solvent	L/S ratio	Temp °C	
64	*Allium cepa* L.(bulbs)	BBD	5–25	100–300	ChCl : urea : H$_2$O	40 : 1–60 : 1	—	116
65	*Cajanus cajan* (L.) Millsp (roots)	BBD	10–30	500 (fix)	1,6-Hexanediol/ChCl 7 : 1 + 30% H$_2$O	5 : 1–15 : 1	50–90	120
66	*Eugenia uniflora* L. (leaves)	CCD	12–38	800 (fix)	Malic acid, lactic acid or ChCl + sugar	1 : 0.0261–1 : 0.0439 (wt/wt)	38–40	117
67	*Hibiscus manihot* L. (flower)	TOD	5–25	400–800	HBDs + ChCl	10 : 1–30 : 1	40–80	118
68	*Hibiscus sabdariffa* L. (calyces)	BBD	3 (fix)	250–550	HBDs + citric acid + 10–50% H$_2$O	—	—	123
69	*Larix gmelinii* (Rupr.) Kuzen. (different parts)	BBD	5–15	230–540	1-Butyl-3-methylimidazolium bromide	15 : 1–25 : 1		124
70	*Morus alba* L. (leaves)	BBD	8–24	600 (fix)	ChCl/glycerol (1 : 2)	15 : 1–20 : 1	45–75	119
71	*Peucedanum praeruptorum* Dunn (radix)	Ortogonal assay	5–15	—	[TMG]CH2CH (OH)COOH 0.4–0.8 M	10 : 1–50 : 1	40–60	125
72	*Scutellaria baicalensis* Georgi (radix)	BBD	5–15	—	ChCl lactic acid 1 : 2, 3 : 1	10 : 1–20 : 1	35–75	121
73	*Toona sinensis* (A.Juss.) M. Roem.	Ortogonal assay	12–20	—	[Bmim]Br 1–2 M	25 : 1–40 : 1	60–80	122

ditional thermal methods like steam distillation and hydrodistillation. Besides the conventional extraction with organic solvents, MASE extraction processes include microwave-assisted hydrodistillation (MAHD) and solvent-free microwave extraction (SFME). Many examples of this kind of extraction are reported in the literature, but only a tiny percentage exploit a DoE approach to optimize the yield of the total extract or of a single metabolite. Table 7 lists the most significant examples.

Almost all the articles reviewed studied the total EO yields as the response. The only exceptions are represented by entries #84 and 85, in which the responses are thymol and 1,8-cineole content, respectively.

As evidenced in Table 7, DoE is mainly applied to optimize the extraction of EOs in MAHD. In this case, the most considered factors are time, power, and L/S ratio, and, less frequently, soaking time. In two reports, authors identify extrac-

Table 7 Synoptic table of the references reviewed related to DoE applied to microwave assisted essential oil extraction

| # | Plant | DoE model | Factors | | | | | | Ref. |
			Time (min)	Power (W)	Solvent	L/S ratio	Soaking time	Moisture content %	
74	*Allium cepa* L. (bulb)	PBD	25–50	350–500	SFME	—	—	20–50	127
75	*Cannabis sativa* L. (inflorescences)	CCD	60–100	1000–1561	SFME	—	—	35–55	42
76	*Cannabis sativa* L. (inflorescences)	CCD	80–140	700–1500	SFME	—	—	13–50	43
77	*Cinnamomum zeylanicum* L. (Bark)	Taguchi based design	40–60	450–800	MAHD	50/1–15/1	5–15 min	—	128
78	*Citrus sinensis* (L.) Osbeck (leaves)	CCD	60–120	300–600	MAHD	2/1–4/1	—	—	129
79	*Glycine max* (L.) Merr. (grains)	FFD	3 (fix)	480 (fix)	IPA, EtOH ± water	5 : 1 (fix)	0–40 min	—	130
80	*Pinus pumila* (Pall.) Regel (Needls)	BBD	20–40	385–700	SFME	—	—	30–50	131
81	*Rosmarinus officinalis* L. (leaves)	CCD	25–85	550–1150	MAHD	0–3/1	—	—	132
82	*Syzygium aromaticum* (L.) Merr. & L.M.Perry (stems)	CCD	40–120	300–600	MAHD	1.5 : 1–3 : 1	—	—	133
83	*Taxus chinensis* (Rehder & E.H. Wilson) Rehder (leaves)	CCD	10–20	400–600	DCM	15 : 1–25 : 1	—	—	134
84	*Trachyspermum ammi* L. (Friuts)	CCD	50–120 (×1 or 2)	1000–1560	MAHD	24/1–5/1	0–4h	—	135
85	*Wurfbainia vera* (Blackw.) Skornick. & A.D.Poulsen (leaves)	BBD	40–120	140–280	MAHD	10 : 1–15 : 1	—	—	136
86	*Xanthoceras sorbifolium* Bunge (seeds)	BBD	60–100	200–300	MAHD + NaCl	3 : 1–5 : 1	—	—	137
87	*Zingiber officinale* Roscoe (rhizome)	FFD	10–30	288–640	SFME	—	—	—	138

tion time as the most important parameter (entries #77 and 84), followed by microwave power. Experimental conditions for optimal total yield generally mention the longest extraction time and highest microwave power values, whereas the L/S ratio and soaking time parameters seem case specific. Furthermore, two different works also focused on optimizing the content of specific metabolites in the EOs, *e.g.*, thymol (entry #84) and 1,8-cineole (entry #85). In both cases, the authors recommend mild extraction conditions (lower power in the first case and shorter time in the second), suggesting that an appropriate extraction method should consider the specific metabolites' stability during setup. Interestingly, the analysis of the process factors studied in the articles reviewed in this section (Table 7) showed that only one report (entry #86) mentioned temperature as an important factor, while raw material particle size appeared three times (entries #74, 83, and 87).

One paper (entry #86) reported that amounts of NaCl in water positively correlate with the extraction yield of seed oil from yellow horn (*Xanthoceras sorbifolium* Bunge). The presence of salt is an unusual factor, justified by the authors claiming that the salt is a green demulsifying agent of water-in-oil emulsions. The demulsification efficiency was maximized with 24 g L^{-1} salt in water and the authors observed that the extraction yields abruptly declined at NaCl concentrations higher than 25 g L^{-1}. Such a result is a clear demonstration of the efficacy of the adoption of DoE/RSM in MAHD.

The other extraction method peculiar to EOs is SFME, where the most considered factors are time, microwave power, and sample moisture content. As already observed in MAHD, also in SFME, the best values of power and time are in the upper part of the ranges of variation considered, only the extraction duration in this case is usually much shorter than in MAHD.

Some papers have also reported microwave-assisted extraction of EOs with organic solvents (IPA, EtOH ± water entry #79, DCM entry #83). One report (entry #79) describes a MASE approach using isopropyl alcohol and water, allowing yields comparable to those obtained with hexane, the most widely used solvent for extracting edible oils. Consistently, alcohols represent a viable alternative to replace hexane as an extractive solvent for edible oils in MASE.

Finally, although it is not possible to make comparisons between the results obtained through MAHD and SFME, since the biomasses considered in the reviewed works are different, we propose a general reflection on the improvements shown by microwave-based procedures compared to classical extraction methods. MAHD and SFME are environmentally friendly and sustainable approaches, as they do not use organic solvents.

A survey of the use of DoE in MASE

The survey of recent literature presented in previous paragraphs allowed us to draw general reflections about aims, experimental conditions and outcomes of DoE application to MASE.

First, the aim of all the studies reviewed is to set up an extraction method capable of maximizing the outcomes, often keeping in mind the repeatability of the newly set up procedure. To this aim, in 40 articles (45%) the application of a DoE model is performed only after preliminary experiments aimed at screening the influencing factors and their optimal ranges. Therefore, this first step is often overlooked, as less than half of the analyzed papers perform it, suggesting that more attention should be paid to this topic. Thus, this initial step allows the researcher to obtain more significant results, permitting not only to focus on really influencing factors, but also to study their range in a more deepened way. Moreover, among the articles related to extractions with ILs and DES, initial screening often considers only the solvent. Although this factor is crucial, it's also important to underline that in these extractions a deeper preliminary analysis of the other factors should be done.

Another issue associated with MASE is related to the oven. Thus, although in many cases a professional microwave oven is exploited, *e.g.*, MAS-II microwave systems (Shanghai Sineo), Ethos Easy and NEOS systems (Milestone Srl), and MARS /MARSX systems (CEM), the use of adapted domestic oven is still accepted. The use of this kind of apparatus should be limited if not completely avoided, as the temperature and pressure control is often inaccurate. More generally, the most exploited ovens are multimodal apparatuses equipped with two magnetrons, working at a frequency of 2450 MHz.

As mentioned before, microwave heating applied to the extraction of natural matrices can be considered a green approach not only for the reduction of time and use of hazardous solvents, but also for the lower energy required compared to other techniques. This last aspect is guaranteed by both the drastic reduction in time and the gram to kilo scale in which the extractions are usually performed.[15,16] Unfortunately, this last aspect is not always considered during the set-up of a new method, since the amount of natural matrix exploited in this phase typically ranges from hundreds of milligrams to a few grams, thus limiting the energy saving usually associated with MASE. Consistently, curtailing the number of experiments required to identify the best extraction conditions and applying a DoE model is mandatory to make the most of MASE potential.

In this context, many different experimental designs have been exploited, but two were the most represented ones, *i.e.*, Box–Behnken (39 times), and central composite (26 times). As mentioned before, both these designs allow computing canonical quadratic models used to describe the system fully by RSM. These models are the most popular because they are implemented in all commercial software and allow studying up to 4–5 factors easily.

Interestingly, the study of the factors considered, particularly the relationship between microwave power and temperature evidenced the need for considering both these factors simultaneously.

In the reports reviewed, only one of these two factors is generally considered in the DoE, and the selection made is mainly dependent on the kind of experiment performed. Microwave power control is judged more critical than temperature control in general solvent extraction and extraction of essential oils, while temperature control is considered of primary relevance in extraction performed with ILs or DESs. This may be due to the already discussed influence of temperature on the solvents' viscosity and stability of some DESs, however, these problems are not relevant to methods of extraction performed with standard solvents.

A final issue to be highlighted is the DoE model validation. Out of the 87 articles reviewed, only 49 (56%) mentioned model validation. This picture is very common, and already discussed in previous reviews.[38] It is worth underlining here that the application of DoE to collect experimental data is always effective (*i.e.*, allows to reduce the amount of work while providing the best information available), and it can be concluded by a mere description of the results after model computation through the ordinary least squares method. In this case, the experimenters provide a picture of their results as obtained under specific conditions applied during the working sessions but cannot provide evidence of the prediction ability of the model computed. On the other hand, when the model is validated, the experimenters may claim that the model describes the process over the entire experimental domain and can appraise quantitative predictions and experimental variance on the outcome of experiments not performed.

Conclusions

The MASE procedure is well suited for use in the drug discovery phase from natural sources because it offers numerous advantages over conventional techniques including a shorter sample processing time, lower amounts of solvent used, wide options of using green solvents, and greater flexibility allowing the users to maximize the extraction efficiency by modulating the factors that regulate the process control. In the set-up of extraction protocols, several factors should be considered simultaneously and for this reason the OFAT approach may severely limit the technique's advantages. As an inherently multifactorial technique, the only way to apply the MASE procedure, fully exploiting its potential, is by using the DoE approach. Such an approach, besides allowing to reduce to a minimum the number of experiments in method development, guarantees to obtain the maximum amount of information of better quality. Regrettably, although DoE has proven its effectiveness in many applied research fields ranging from psychology, agriculture, and engineering to analytical and medicinal chemistry, its application to MASE is still limited. The main advantage of DoE is associated with the ability to make consistent predictions about time, resources, and effort for reaching the research goal. DoE brings with it a deeper knowledge and understanding of the process being studied by modeling the effects of factors and their interactions. The knowledge of the role of the process factors is fundamental for optimizing the extraction and it allows one to minimize the number of experiments required even if a small amount of natural matrix is available.

In summary, combining MASE and DoE is not yet widespread, but, as determined by the literature survey and in the opinion of the authors, this could be the winning strategy to speed up the NADD process.

Author contributions

Conceived the literature review. V.C and G.M. conducted the literature review. V.C and G.M. wrote the literature review with input from E.M. and S.C. E.M. and S.C. conceived the analysis; V.C and G.M. wrote the paper with input from all co-authors.

Conflicts of interest

There are no conflicts to declare.

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