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Multi-objective optimization of microextraction procedures

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ABSTRACT

Optimization of extraction process requires finding acceptable conditions for many analytes and good performance in terms of process time or solvent consumption. These optimization criteria are often contradictory to each other, the performance of the system in given conditions is good for some criteria but poor for others. Therefore, such problems require special assessment tools that allow to combine these contradictory criteria into single score to find “the golden mean”. This contribution summarizes the examples of approaches that are used for multi-objective optimization. Derringer`s desirability functions are used for large variety of microextraction techniques optimizations. Finding Pareto-optimal solutions allows to easily separate conditions that are definitely not acceptable. Alternative solution is application of multi-criteria decision analysis for microextraction processesoptimization.

Keywords: Pareto optimality; Derringer’s desirability; Multicriteria decision analysis; Extraction; Liquid-phase microextraction.

1. Introduction

In case of microextraction techniques type of extraction solvent, its volume, sample volume, temperature during extraction process, addition of inorganic salt and many other, often microextraction technique-specific, parameters need to be optimized. The aims of these optimizations are to obtain good recoveries of analytes, acceptable resolution of separation,

short extraction time, the best fit to green analytical chemistry principles etc. It should be noted that these aims are often contradictory, as improvement of one output means deterioration of another one. In such cases, dedicated approaches for optimization processes need to be applied. A simplified scheme of multivariate and multi-objective optimization of microextration techniques is presented in Figure 1.

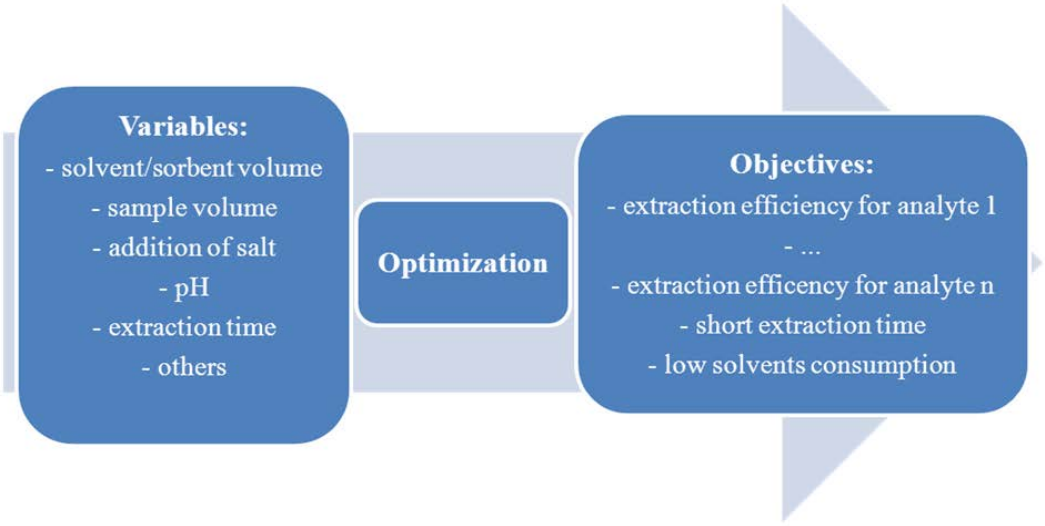

Figure 1. Examples of variables and objectives for optimization processes in area of microextraction techniques

Multivariate optimization is relatively widely applied in analytical chemistry and it is aimed at selection of few variables at the same time that are relevant to response [1]. In this contribution we review the methodologies in which optimization is performed for few variables with two or more responses at the same time.

2. Why multi-objective optimization?

Development of analytical procedures for single analyte is rather rare but they are sometimes developed for determination of active substances in pharmaceutical products. For two and more analytes extraction procedure might need multi-objective optimization. To show it, let us consider tutorial, simplified case for microextraction procedure optimization. Let us assume a situation where two analytes X and Y are determined with procedures in conditions A and B. In conditions A the responses are 100 and 10 for X and Y, respectively. In conditions B the responses are 80 and 15 for X and Y respectively. At the first glance it is not clear, which conditions are better. In some cases authors apply an approach based on

summing of peak areas. In presented case study, the sum of responses for conditions A are 110 and for conditions B they are 95. From this reasoning it can be concluded that conditions A are superior. On the other hand, conditions B are just 20 % worse for analyte X and 50 % better for analyte Y. This shows that summing of responses approach is not adequate approach. What is more, summing of responses on case of conditions C, where X response is 100 and Y response is 0 or close to 0, still shows that conditions C are superior over B. This situation is not acceptable, as the procedure is being developed for two analytes.

An approach to deal with two analytes optimization of extraction procedure can be multiplication of extraction recoveries (MER)[2]. In this approach for optimization of extraction technique, multiplication of responses favors conditions where both responses are high. In case of low response of one of analytes MER value for entire system would be also low.

The system is getting more complex to be optimized if there are more analytes determined during extraction procedure. In such cases multi-objective optimization methods should be applied. The results of their application are often input to Design of Experiment (DoE) and are interpreted with Response Surface Methodology (RSM), which will not be discussed in this contribution. The main aims of the application of DoE are identification of important factors during procedure optimization, establishment of relations between variables and finding mathematical relationship between the variables and response. Changing all variables at the same time results in savings in time and labor [3]. For excellent reviews on this topic please refer to[4, 5]. As presented in figure 1. multivariate optimization is applied to combine many relevant variables. During multiobjective optimization it is aimed to combine multiple outputs together.

Microextraction optimization itself usually can be considered as multioutput system. The recoveries/responses/peak are for many analytes are obtained, other optimization objectives are low solvent consumption/green solvent application, short extraction time and others.

3. Derringer's desirability function

Derringer's desirability function is applied to combine many responses of the optimized system both at the stage of sample preparation and chromatographic separation. Derringer's desirabilities are calculated for each of the assessment criteria. Desirability function (d_i) is continuous, linear or exponential function and varies between 0 (completely undesirable response) and 1 (completely desirable response). If the response $y_i(x)$ has to be maximized

[6], like in case of peak areas, recoveries, signal to noise ratios, chromatographic resolution, the equation is used:

$$d_i = \begin{bmatrix} 0 & if\ y_i(x) < L_i \\ \left(\frac{y_i(x)-L_i}{U_i-L_i}\right)^S & if\ L_i \le y_i(x) \le U_i \\ 1 & if y_i(x) > U_i \end{bmatrix} (1)$$

Where U_i and L_i are the values of response of respectively upper and lower limits of acceptability range. S is coefficients that allow to assign the importance on the value of response to be close to maximum. For the response that has to be minimized, such as relative standard deviation, analysis time, applied equation is following:

$$d_i = \begin{bmatrix} 0 & if\ y_i(x) > U_i \\ \left(\frac{U_i-y_i(x)}{U_i-L_i}\right)^T & if\ L_i \le y_i(x) \le U_i \\ 1 & if\ y_i(x) < L_i \end{bmatrix} (2)$$

T is coefficient that allows to put higher or lower importance on the response value to be close to minimum. Values of T coefficient larger than 1 indicate high importance of d_i to be close to minimum, values lower than 1 indicate low importance of such a necessity, while T = 1 is for linear function between U_i and L_i.

Global desirability (D) is the combination of individual desirability functions (d_i) and is calculated with following equation:

$$D = (d_1^{r_1} \times d_2^{r_2} \times \ldots \times d_n^{r_n})^{\frac{1}{\Sigma ri}} (3)$$

where, r_1, r_2 (…) r_n are weights of respective desirability functions. The value D = 1 means that global desirability is maximized, all criteria are within desired range. The value of D = 0 indicates that at least one of criteria is within undesirable range and therefore the global system response cannot be accepted.

Table 2 shows some of the examples of application of Derringer's desirability functions. It can be concluded that the simplest way to set the desirable and undesirable response values is to select appropriate extreme values – for maximized response maximum and minimum values, for minimized response minimum and maximum values. In case of no other user preference, it is easy to apply linear desirability function between desired and undesired values. Desirability function allows to combine into a single score any number of optimization criteria. Apart from criteria referring to chromatographic or extraction performance, other parameters such as solvent or energy consumption can be included.

Derringer's desirability function is convenient method to combine multianalyte outputs into a single value that is an input data to RSM.

One of the major advantages of Derringer's desirability is that global desirability in unacceptable if at least one of the criteria falls into non-desirable range. Another advantage is that user can define the function between desirable and non-desirable range according to his preferences. There is also the possibility to differentiate the importance of criteria by assigning them different weights. The disadvantage is the fact that defining desirable, non-desirable ranges and desirability function requires some knowledge on the system or experience from the user. The user has to know what are desirable and non-desirable recoveries, analysis time or other parameters.

For the (probably oversimplified) case study presented in the section 2 Derringer's desirability functions can be calculated. To keep the considerations simple, for these three conditions, the desirable ranges for X and Y are maximum values and undesirable ranges are 0 (no chromatographic peak). The function itself, is assumed to be linear between desirable and undesirable range and responses for both compounds are equally weighted. The summary of assumptions is presented in table 1.

Table 1. Individual desirabilities d(Y), d(X) and global desirability D for hypothetical case study.

	X	**Y**	**d(X)**	**d(Y)**	**D**
conditions A	100	10	1	0.667	0.817
conditions B	80	15	0.8	1	0.894
conditions C	100	0	1	0	0
desirable response	100	15			
undesirable response	0	0			

According to the assumption of undesirability the conditions C cannot be accepted, as global desirability equals to 0. In contrary to the approach presented in section 2, of summing chromatographic responses, conditions B are indicated as optimal. In this case the response for Y is maximized, while response for X is close to maximum. These considerations show that Derringer's desirability functions are more appropriate tool to assess multi-response chromatographic system, than sum of responses approach.

More real life example is optimization of dispersive liquid-liquid microextraction (DLLME) in terms of extraction and dispersive solvents volumes to obtain satisfactory extraction of compounds, responsible for the deterioration of wine [7]. Obtaining the best recoveries for 8 compounds were the input data. The desirable response was assumed to be

100%, while undesirable response was set to recovery under 50%. Figure 2 presents the global desirability response in the function of extraction and dispersive solvents volumes. It is clear that for volumes of extraction solvent below ~110 µL the recoveries for at least one of the analytes are below 50% and the global desirability response becomes undesirable for higher volumes of dispersive solvent. What is also interesting authors decided to give to six compound weight equal to 1, while remaining two were assigned with weights equal to 10, as they have lower olfactory threshold, so can contribute more to deterioration of wine. In practice it means that the extraction procedure is optimized more towards these two compounds than remaining six. The highest global desirability was for 1.43 mL of dispersive solvent and 173 µL of extraction solvent.

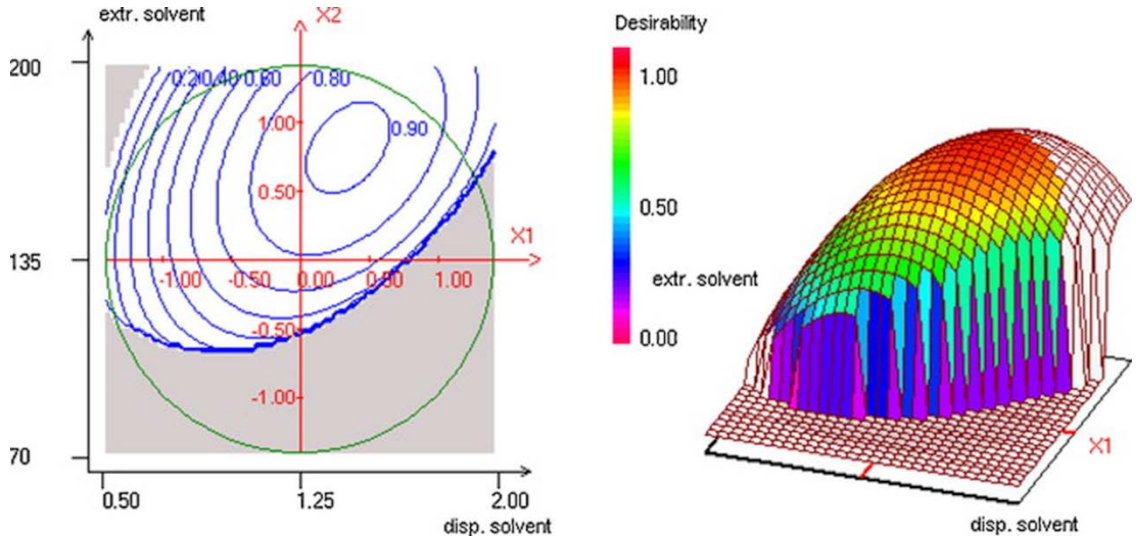

Figure 2. Response surface for global desirability for DLLME optimization of extraction and dispersive solvents volumes. Reprinted from Pizarro, C., Sáenz-González, C., Pérez-del-Notario, N., & González-Sáiz, J. M. Development of a dispersive liquid–liquid microextraction method for the simultaneous determination of the main compounds causing cork taint and Brett character in wines using gas chromatography–tandem mass spectrometry. *J. Chromatogr. A, 1218*(12) (2011) 1576-1584with permission from Elsevier.

Table 2. Application of Derringer's desirability functions for microextraction optimization

Goal	Microextraction technique	Optimization criteria with optimized values	Desirability ranges	Remarks	Ref.
Determination of N-methylcarbamate insecticides in water samples using DLLME combined with HPLC	DLLME	• volume of extracting ($CHCl_3$): 126 µL • volume of dispersing solvents (ACN): 1.5 mL • pH: neutral • ionic strength: 4.7% (w/v) NaCl • extraction time: 1 min • centrifugation time: 10 min • centrifugation speed: 4000 rpm/min (For desirability score of 1.0)	DF settings for each dependent variable of ER% are depicted at the right hand side of desirability of: • 1.0 was assigned for maximum ER% (91.0%) (very desirable) • 0.5 for middle (61.0%) • 0.0 for minimum (31.0%) (undesirable)	DF was used to identify optimum ER% by calculating specific variables optimization simultaneously. LOD = 0.0001 and 0.0005 µg/mL RSD = 2.18–5.06%	[8]
Determination of seven UV filters extensively used in cosmetic products in environmental water samples using IS-MSA-DLLME-GC-MS	IS-MSA-DLLME	• volume of extraction solvent (trichloroethylene): 1.05 mL • dispersive solvent (acetone): 600 µL • derivatization agent (BSTFA): 350 µL • pH: 7 • ionic strength: 0.7 mol/l NaCl • stirring time: 160 s	Desirable and undesirable responses are maximized and minimized, respectively.	Relative peak areas and relative standard deviations were combined into single score RSD (intra-day) = 4.0 to 13.7% RSD (inter-day) = 5.9 to 16.8% EF = 8.5 and 12.9 ER = 82 to 111% LOD = 0.023–0.16 µg/L	[9]
Determination of thymol and carvacrol in pharmaceutical samples with UAME-NMSPD-HPLC-UV	UAME-NMSPD	• ultrasonic time: 10 min • pH: 3 • amount of adsorbent (NiS-NP-AC): 0.011 g • volume of extraction solvent: 600 µL • ionic strength: no addition of salt ([NaCl] = 0%)	Desirability assigned for ER: • 1.0 for maximum (95.3%) • 0.5 for middle (69.4%) • 0.0 for minimum (43.5%)	LOD (thymol): 0.23 µg/L LOD (carvacrol): 0.21 µg/L RSD < 4.93%	[10]
Determination of organophosphate esters (TPP, TBP, TCEP, TCPP, TDCPP, TBEP, TPhP, EHDPP, TCP) in airborne PM: MAE-SPME-	MAE-SPME	• extraction time: 45 min • extraction temperature: 80 ^{o}C • percentage of sodium chloride: 10 %	Not stated	The chromatographic responses for all analytes are integrated with DFLLOQ = 0.5 ng/mL (TDCPP) LLOQ = 0.1 ng/mL (other analytes)	[11]

GC-MS/MS				Precision: TDCPP - 1.0–12.4% Other analytes - 2.3–15.2%	
Simultaneous determination of benzothiazoles, benzotriazoles and benzosulfonamides by SPME-GC–QqQMS in environmental aqueous matrices and human urine	SPME	• extraction time: 40 min • pH: 7.1 • NaCl: 6.0 %	Desirablity ranges not stated. Chromatographic responses of 18 pesticides were combined into single score with DF	In all the matrices tested the lowest LOD and LOQ values were obtained for 2-MeSBTH	[12]
Simultaneous determination of carcinogenic PAHs in environmental samples using AuNPs using SPE-GC-UV	SPE	• adsorption vortex time: 7.22 min • desorption solvent: 5 mL of 1,3-propanedithiol • acceptor volume solvent (n-nonane): 15 mL • methanol volume: 44 mL • desorption vortex time: 9.63 min	Desirable response – max. Nondesirable response – min. The responses for 13 PAHs are combined into single score	RR = 76.2–101.2 % (tap water) RR = 78.4–104.2 % (well water) RR = 74.3–100.2 % (farm water) RSD = 1.56–6.93% (tap water) RSD = 1.89–7.46 % (well water) RSD = 2.56–8.89 % (farm water)	[13]
Determination of OPFRs analysis in environmental aqueous matrices using -GC-PTV -MS/MS	MEPS	• evaporation time: 0.2 min • evaporation temperature: 60^{o}C • initial temperature: 60^{o}C • solvent vent flow: 50 mL/min • injection speed: 50 µL/s	Desirability ranges not stated Combines chromatographic responses for 10 flame retardants.	LOD = 2.7–99 pg/mL (tap water) LOD = 2.9–97 pg/mL (river water) LOD = 3–107 pg/mL (wastewater) LOQ = 0.01–0.2 ng/mL	[14]
Gliclazide, glibenclamide and glimepiride determination in serum of diabetic patients using DLLME-HPLC-UV	DLLME	• type and volume of extracting solvent: 100 µL of dichloromethane • type and volume of dispersing solvent: 1000 µL of acetonitrile • protein precipitation: no protein precipitation	Recoveries for 3 compounds were simultaneously optimized. Max. desirability function obtained D=0.910. Desirability ranges are not stated.	LOQ = 0.11µg/mL (gliclazide) LOQ = 0.10 µg/mL (glibenclamide) LOQ = 0.14 µg/mL (glimepiride) Recoveries:95.7 - 98.0%	[15]
Determination of organotin compounds (butyl-, phenyl- and octyltin compounds) in sediment samples using DLLME-GC-PFPD	DLLME	• type and volume of extraction solvent: 413 µL methanol • type and volume of disperser solvent: 34 µL tetrachloroethylene	Responses for 7 organotin compounds were combined. Desirability ranges are not stated.	LOD = 0.3 - 1.0 ng/L RSD = 2 - 6% Recoveries = 70 - 98%	[16]
Determination of phthalates in wine using HS-SPME-GC-	HS-SPME	CW-DVB fiber: • temperature: 70^{o}C	Max. is desirable response, min. is undesirable response.	In this study apart from extraction conditions, SPME fibers were	[17]

MS		• sample volume: 3.5 mL • NaCl concentration: 3.6 M <u>PA fiber:</u> • Temperature: 70°C • sample volume: 4.0 mL • NaCl concentration: 2.6 M <u>PDMS-DVB fiber:</u> • Temperature: 70°C • sample volume: 3.0 mL • NaCl concentration: 5.5 M		selected for best performance towards phthalate compounds.	
Simultaneous chloropropanols(1,3-DCP, 2,3-DCP, 3-MCPD) determination in soy milk and other aqueous matrices(water and beverages)using UA-DLLME-GC-MS (water and fruit juices) and UA-DLLME-GC-MS/MS (milk and soy-milk)	UA-DLLME	<u>Water and fruit juices:</u> • type and volume of extraction solvent: 60 µL of chloroform • type and volume of dispersive solvent: 0.9 mL of acetonitrile • amount of derivatization agent: 50 µL of HFBI • temperature: 40°C • pH: 6 • ionic strength: 1.8 g of NaCl <u>Milk and soy-milk:</u> • type and volume of extraction solvent: 100 µL of chloroform • type and volume of dispersive solvent: 2 mL of acetonitrile • amount of derivatization agent: 50 µL of HFBI • temperature: 30°C • pH: 7 • ionic strength: no salt	Responses are peak areas for MCPDs. Desirability ranges are not stated	LOD = 0.2–1.8 µg/L (water) LOD = 0.5–15 µg/L (fruit juices) LOD = 0.9–3.6 µg/L (milk) LOD = 0.1–1.0 µg/L (soymilk) Recovery = 98–101% (water) Recovery = 97–102% (juices) Recovery = 99–103% (milk) Recovery = 97–105% (soy beverage) RSD = 1.3 - 4.9% (water) RSD = 2.3 - 5.8% (juices) RSD = 1.0 - 5.7% (milk) RSD = 3.9 - 9.3% (soy milk)	[18]
Simultaneous estrogens (estrone, 17β-estradiol, estriol, and 17α-ethynylestradiol) determination in wastewater samples by IS-MSA-DLLME-GC-MS	IS-MSA-DLLME	• extraction solvent volume: 250 µL of chloroform • disperser solvent volume: 200 µL of acetone • pH: 8 • agitation time: 50 s	Maximum analytical signal is desirable response, minimum analytical signal is undesirable response.	LLODs = 11 - 82 ng/L LLOQs = 37 - 272 ng/L RSDs ≤7.06% (intra-day) RSDs ≤7.11% (inter-day)	[19]
Determination of six	AA-DLLME-SFO	<u>AA-DLLME-SFO optimization:</u>	Several responses were	Comparison of two extraction	[20]

veterinary pharmaceuticals (albendazole,chloramphenicol, trimethoprim, enrofloxacin, oxitetracyclineandnicarbazin) in egg using AA-DLLME-SFO-HPLC-UV	vs. DLLME	• volume of water: 1140 µL • amount of $ZnSO_4$: 125 mg • volume of acetonitrile: 1175 µL • volume of methyl alcohol: 1200 µL • volume of propnone: 740 µL • amount of sample: 1.00 g of homogenized egg • volume of 1-dodecanol: 50 µL DLLME optimization: • volume of acetonitrile: 1840 µL • volume of dichloromethane: 160 µL • re-suspended mixture: acetonitrile and sodium phosphate buffer 10 mmol/LpH = 3.50 (30:70 v/v)	selected for the optimization: peak areas and peak widths	methodologies: AA-DLLME-SFO and DLLME. Extraction of more hydrophobic analytes with recoveries greater than 80% is possible by AA-DLLME-SFO, while more hydrophilic by DLLME. LOQs = 0.016 – 0.92 µg/g LODs = 0.0056 – 0.32 µg/g	
Volatile compounds determination in tomato juice using SPME-GC-MS	SPME	*Cold break* treatment optimization: • temperature: 67°C • time: 24 min *Hot break* treatment optimization: • temperature: 86°C • time: 3.5 min	Peak areas for volatiles were desirable if ≥ 0.9max. or undesirable if ≤ 0.1min.	The aim of this work is the optimization of the blanching thermal treatment (*cold break* and *hot break*) parameters of tomato juice, using as markers the volatile compounds evaluated bySPME.	[21]
OPPs (Mala, Diaz, Phos, Chlor) determination in aquatic samples (well, tap, river and mineral) using MSPE-HPLC–UV	MSPE based on Fe3O4/C	• amount of adsorbent: 97.4mg of Fe_3O_4/C • pH: 9.16 • equilibrium time: 0 min • ionic strength: 10 mmol/L	Chromatographic responses for 4 compounds were maximized, extraction time was minimized, pH, amount of salt and sorbent should be in desired ranges	LLOD = 4.3 – 47.4 pg/mL EF = 330 – 1200 COD = 0.9949 – 0. 9996 LOQ = 14 – 158 pg/mL RSD = 3.7 – 6.6 % EF = 330 - 1200	[22]
Neuroendocrine tumormarkers (HVA, VMA, 5-HIAA) assayin human urine using SPME-GC-QqQMS	SPME	• extraction temperature: 40°C • extraction time: 25.8 min • concentration of NaCl: 9.5 %	Maximum response value is desirable response. Minimum response is undesirable	LOD = 1.3 µg/L (HVA) LOD = 0.046 µg/L (VMA) LOD = 24.3 µg/L (5-HIAA) RSD = 0.5 - 8.9% The chromatographic responses for three analytes are combined into single response	[23]
Multi-class pesticides	DI-SDME	• extraction solution volume: 9	It is not stated how recoveries	LOD = 0.14–169.20 µg/kg	[24]

determination in mango using DI-SDME-GC–MS		mL • sonification time: 15 min • sample weight: 3 g • drop volume: 2 µL of toluene • extraction time: 30 min • pH: without adjustment • extraction temperature: 45^{o}C • stirring rate: 700 rpm • ionic strength: 0 % NaCl	for many pesticides are recalculated into desirability	RSD = 0.7 – 19.1% Recovery = 69 – 119% EF = 20 – 722	
Simultaneous AMB and NIF determination in plasma samples using IS-USAEME-HPLC-UV	IS-USAEME	• extracting solvent volume: 45 µL of 1-octanol • ionic strength: 18.95% (w/v) • sonication time: 2.58 min • centrifugation time: 3 min	Responses for AMB and NIF are maximized, centrifugation time is minimized, while ionic strength, extractant volume and sonication time are aimed to be within given ranges.	LLOD = 0.17 ng/mL (AMB) LLOD = 0.15 ng/mL (NIF) LOQ = 0.569 ng/mL (AMB) LOQ = 0.502 ng/mL (NIF) RSD = < 5.2% (both components) ER = 82.6 % (AMB) ER = 66.7 % (NIF)	[25]
Simultaneous seven organic UV filters (BPN, MBC, OCR, BMP, OMC, OS, HMS) determination in urine samples usingDLLME-HPLC-DAD	DLLME	• type and volume of dispersant solvent: 0.5 mL of acetonitrile • type and volume of extraction solvent: 70 µL of carbon tetrachloride • pH: without adjustment • ionic strength: NaCl 10% (w/v)	Peak areas of 7 UV filters are input data to calculate desirabilities and global desirability. Max. peak area was desirable response, while half of max. peak area was undesirable response	Recoveries = 86.9 - 97.3% LOQ = 3 - 45 ng/mL RSD = < 5 - 8% EF = 44.4 – 48.0	[26]

ABZ – albendazole; **AMB** - amlodipine besylate;**AuNPs** - gold nanoparticles; **BBP** – butylbenzylphthalate; **BMP** – methoxydibenzoylmetane; **BPN** - benzophenone-3; **BSTFA** - N,O-bis(trimethylsilyl)trifluoroacetamide; **CAP** – chloramphenicol;**Chlor**– chlorpyrifos;**CW-DVB** - carbowax-divinylbenzene; **DBP** – dibutylphthalate; **DEHP** - di(2-ethylhexyl)phthalate; **DEP** – diethyl phthalate; **DES** – method based on deep eutectic solvent;**DI** – Direct Immersion; **Diaz** – diazinon; **DLLME** – Dispersive Liquid–Liquid Microextraction; **DMP** – dimethylphthalate; **DNC** - *N*,*N*′-bis(4-nitrophenyl)urea); **DOP** - di-*n*-octylphthalate;**ECs** - emerging contaminants; **EF** - Enrichment factor; **EHDPP** – 2-ethylhexyl-diphenyl phosphate; **ENR** – enrofloxacin; **ER** – Extraction Recovery;**GC** – Gas Chromatography; **HFBI** - *N*-heptafluorobutyrylimizadole;**HF-LPME** - Hollow fiber liquid phase microextraction**; 5-HIAA** - 5-hydroxyindoleacetic acid;**HMS** – homosalate; **HPLC** – High Performance Liquid Chromatography; **HVA** - Homovanillic acid; **IS** – In syringe; **LOD** – Limit of Detection; **LLME** – Liquid-Liquid Microextraction; **LLOQ** – Low Limit of Quantification; **MAE** - Microwave-Assisted Extraction; **Mala** – malathion; **MBC** - 4-Methylbenzilidene camphor; **MEPS** - Microextraction by Packed Sorbent; **MS** – Mass Spectrometry; **MSA** - magnetic stirring-assisted; **MS/MS** – tandem mass spectrometry; **MSPE** - Magnetic Solid Phase Extraction; **NIF** – nifedipine;**NMSPD** - nanomaterial solid phase dispersion; **OCR** – octylcrylene; **OMC** – octylmethoxycinnamate; **OPFRs** - Organophosphate Ester Flame Retardant;**OPPs** – Organophosphorus Pesticides;**OS** – octyl salicylate; **OTC** – oxitetracycline; **PA** – polyacrylate; **PAHs** - Polycyclic Aromatic Hydrocarbons;**PDMS-DVB** - polydimethylsiloxane-divinylbenzene; **PFPD** - Pulsed flame photometric detection**; Phos** – phosalone; **PM** - Particulate Matter; **PTV** - Programmed Temperature Vaporization injector;**QqQMS** - triple quadrupole mass spectrometry; **R_D**- desirability function;**RR** - Relative Recoveries; **RSD** – Relative Standard Deviation; **SDME** – Single Drop Micro-extraction;**SFO** – Solid Floating Organic;**SPE** - Solid-phase Extraction; **SPME** - Solid-phase Microextraction; **TBEP** - tributoxyethyl phosphate; **TBP** - tri-n-butyl phosphate; **TCEP** - tris(2-chloroethyl) phosphate; **TCP** - tricresyl phosphate (TCP); **TCPP** - tris(1-chloro-2-propyl) phosphate; **TDCPP** - tris(1,3-dichloro-2-propyl) phosphate;**TEHP** - tris(2-ethylhexyl) phosphate; **TMP** – trimethoprim; **TPhP** - triphenyl phosphate; **TPP** - tripropyl phosphate;**UAME** - ultrasound assistedmicroextraction; **UHPLC** - Ultra-High Performance Liquid Chromatography;**USA**–Ultrasound-Assisted;**USAEM**E – Ultrasound-Assisted Emulsification-Microextraction;**UV** – UV-vis spectroscopy

4. Pareto optimality

The state of the system is Pareto-optimal (sometimes it is called Pareto-efficient) if no criterion can be improved without decreasing efficiency of other criteria. In other words the two solutions that are Pareto-optimal if they are non-dominant one versus another. It should be noted that there can be many points for the systems that are Pareto-optimal and so called Pareto front is formed [27]. To visualize the optimization results for many objectives and at least few variables parallel coordinates plots are used[28]. As two or three dimensional data can be easily visualized with Cartesian coordinate system, it is not possible for datasets of higher dimensionality[29]. Parallel coordinates plot can be used in such cases and it is a set of vertical axes with their number equal to the number of dimensions. On each axis the original data is reflected, usually the range between min and max value covers the entire length of the respective axis. If the solution line (connection of data points on variable axes) is parallel to another one, they do not cross it means that one of them dominates another one. In this way it is convenient to identify Pareto-optimal solutions and in fact, in case of many solutions to the given problem, dominated solutions are usually not shown to increase the clarity of presentation. Removal of other than Pareto-optimal solutions also allows to simplify further considerations. Visualization of Pareto optimal solutions with parallel coordinates plot helps in selection of optimal solution and allows to easily identify dependences between variables and different responses of the system.

Parallel coordinates plot is used for the optimization of derivatization process of chlorophenols and chloroanisoles before SPME extraction and gas chromatographic separation [30]. The objective of optimization is maximization of responses for 8 analytes for changing the temperature and reaction time parameters. The Pareto-optimal conditions and responses are visualized with parallel coordinates plot as shown in the figure 3. For better clarity of the scheme other than Pareto optimal solutions were removed. The results show that short reaction time and high temperature are optimal conditions for tetrachloroanisole and pentachloroanisole derivatization (violet lines in the figure), while low temperature with longer derivatization reaction time are better for remaining analytes (dark blue lines in the figure). Finally, low temperature of 45 ºC and long 25 min time are selected as optimal for derivatization of these groups of compounds and the optimal solution is marked with dashed yellow line in the figure 3.

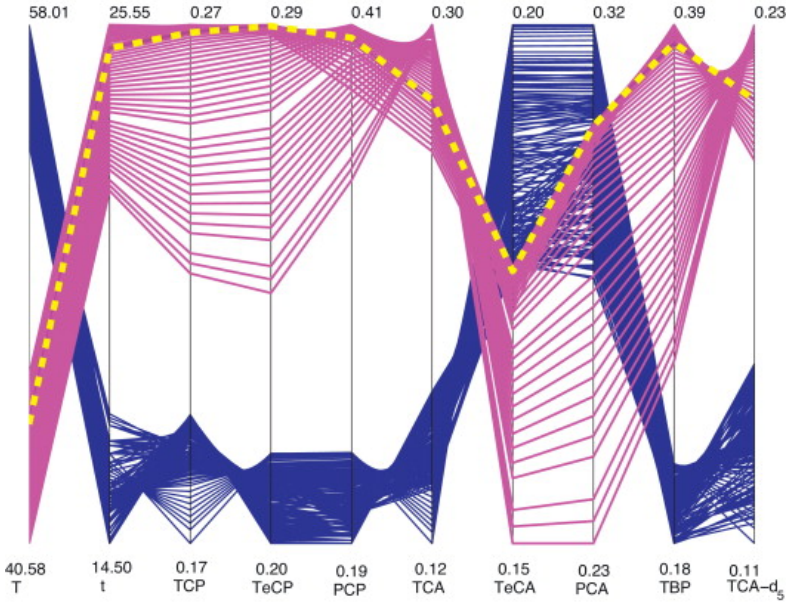

Figure 3. The example of parallel coordinates plot of Pareto front. Reprinted from Morales, R., Sarabia, L. A., Sánchez, M. S., & Ortiz, M. C. Experimental design for the optimization of the derivatization reaction in determining chlorophenols and chloroanisoles by headspace-solid-phase microextraction–gas chromatography/mass spectrometry. J. Chromatogr. A 1296 (2013) 179-195 with permission from Elsevier"

Pareto-optimal solutions are used to find the best conditions in designing of liquid chromatographic separations of phenol and bisphenol-A [31]. The aim is to maximize chromatographic peak areas and minimize retention times by changing mobile phase composition, its temperature and flow rate. The optimal conditions for such a separation process are selected with Pareto front, which is visualized with parallel coordinates plot. From conditions forming the Pareto front, the optimal are arbitrarily selected to maximize the peak areas for both of analytes.

Similar methodology is also used to optimize liquid chromatographic separation, taking into account ruggedness and resolution [32]. This study also shows that Pareto-optimal results are in agreement with results of Derringer's desirability function. Parallel coordinates plot can be obtained with MATLAB, the functions are presented in [33], on the example of optimization of HPLC separation process.

5. Multi-criteria decision analysis

Multi-criteria decision analysis (MCDA) is applied to deal with decision problems with many criteria that are often contradictory to each other [34]. There are several main MCDA algorithms, each of them gives an output in form of single numerical value for every

alternative. This value combines at least few respective assessment criteria[35] and can be treated as useful tool in multi-objective optimization.

The Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) is one of MCDA techniques [36] that has been used for the assessment of extraction in DLLME. From the combination of pairs of 8 extraction solvents and 3 dispersive solvents the most appropriate are selected with the aim of maximization of peak areas and minimization of coefficients of variance for 9 chlorophenols [37].The best overall performance for 9 analytes is for cyclohexane-acetonitrile pair of solvents. Another assessment has been done for environmental and safety hazards criteria to assess the greenness of these solvents. This assessment shows that heptane-acetone is the most favorable option in terms of green analytical chemistry. The third assessment is the combination of two previous ones and it proves that completely different criteria can be successfully combined in single assessment. The first rank in this assessment is also achieved by heptane-acetone pair of extraction and dispersive solvents. This work combines the objective that are stated by purely analytical goals and green analytical chemistry concept.

MCDA was also applied for the selection of derivatization agent for chlorophenols determination with DLLME technique [38]. The objectives of the optimization process were to obtain good derivatization efficiency for every analyte, to obtain good chromatogram without artefacts that would prevent unambiguous chromatogram reading and the agent should be green. Greenness of derivatization agent was defined with few criteria, referring mainly to safety of operation, but also environmental persistence criteria. The most efficient derivatization was obtained with acetic anhydride, the highest chromatogram quality was reached with the mixture of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA)andchlorotrimethylsilane (TMCS) in proportions 99:1, while the greenest agent was N-heptafluorobutyrylimidazole (HFBI).

Another application of TOPSIS includes treatment of peaks areas for eight analytes to obtain a single score, similarly as it is case of application of Derringer's desirability function. The output of TOPSIS application is used to obtain surface response for different volumes of water sample, dispersive and extraction solvents in DLLME [39].The main differences in relation to Derringer's desirability function approach are no need to define desirable and undesirable levels and desirability functions. Therefore, they do not have to be known or stated by the analyst. TOPSIS algorithm maximizes the output for all criteria, is not aimed at reaching the certain levels of criteria, as it is in case of Derringer's desirability.

6. Conclusions

Micro-extraction procedures are multi-objective processes. Apart from optimization goals of good performance for every single analyte, usually short process time and other objectives have to be met. As they may be contradictory, special approaches are needed that allow to simplify multi-objective problem into single objective scenario. The results of application of these tools are often combined with DoE to find the optimal parameters. Application of multi-objective optimization allows to introduce green analytical chemistry to microextraction optimization in very elegant way.

Sample preparation and also chromatographic separations can be optimized successfully with variety of tools, such as Derringer's desirability functions, multicriteria decision analysis or Pareto optimal solutions. On the other hand, multi-objective optimization methods (especially Derringer's desirability functions) are usually insufficiently described to know how they were actually applied.

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