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ORIGINAL PAPER

Profiling of 3,4-methylenedioxymethamphetamine by means of high-performance liquid chromatography

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Abstract An impurity-profiling method for 3,4-methylenedioxymethamphetamine (MDMA) is presented. The impurities of interest were extracted by solid-phase extraction (SPE) on Bakerbond C_{18} spe columns from a weakly alkaline solution (pH 8.5). Development of the extraction conditions covered selection of the buffer for dissolution of the sample and the volume of the eluent used to elute the impurities. An important part of the studies was to optimise the separation conditions, and the simplex method was used for this purpose. Cluster analysis was applied for comparison of samples and its grouping. The developed method was based on the areas of 33 selected peaks corresponding to MDMA impurities. All examined samples were correctly classified into clusters corresponding to the synthetic route.

Introduction

3,4-Methylenedioxymethamfetamine (MDMA) is a synthetic analogue of amphetamine and mescaline, therefore its action is a combination of the stimulating effect of amphetamine and the hallucinogenic effect of mescaline. The action of MDMA on an individual is difficult to predict, because it depends not only on the dose but also on the expectations of the user and different external conditions [1]. The physical effects include increased heart rate, sweating, hypothermia, and increased body temperature, even to 43°C. In some cases severe physical complications have been reported including acute renal failure and cerebral haemorrhage. In most cases death is caused by hypothermia. The psychological effects can be both positive and negative. The positive effects can include compassion, decreased fear, euphoria, and relaxation. Moreover, some users experience empathogenesis, a feeling of emotional closeness to others, and very often the senses of touch, taste, vision, and smell are enhanced. The negative effects include: amnesia, confusion, depression, insomnia, panic attacks, and paranoia. Some users experience hallucinations, which can lead to dangerous, unusual behaviour and death. Long-term effects of MDMA abuse are linked with insomnia, depression, hallucinations, and panic attacks.

MDMA is often called *ecstasy*, although this name also covers other derivatives of 3,4-methylenedioxyamphetamine. On the drug market, MDMA is available as a hydrochloride, and is distributed in the form of tablets in a variety of colours, shapes, sizes, and embossed logos.

Ecstasy tablets are a mixture of many substances. Psychoactive substances such as caffeine or paracetamol and the neutral additives such as sugars, starch, or fatty acids can be added to the main component before compression into tablets. Moreover, the impurities formed during production or present in precursors, reagents, and solvents can be found in the final product. The primary impurities can also react and be transformed in each step of production. The conditions of storage, light, heat, or humidity, can lead to the formation of new impurities [2–5].

According to ENFSI Drugs Working Group definition, profiling is the use of methods to define the chemical and/or physical properties of a drug seizure for comparing seizures for intelligence (strategic, tactical) and evidential purposes. Many techniques can be used either alone or in combination, however, the profiling system needs to be fit for purpose. To be fit for purpose a profiling system must have a defined purpose, include an understanding of sample variation within and

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between batches, and must include reporting tools, systems, or mechanisms which allow the results to be reported and understood by the end user. This means that profiling is more than an analytical method.

One of the most important part of MDMA profiling is analysis of its organic impurities. The qualitative and quantitative composition of the impurities can be shown in a form of chromatogram, electropherogram, FT-IR or Raman spectra, etc. These plots show the impurity pattern (profile) in a sample [6]. Profiling gives additional information on reagents, catalysts, and the method of purifying the crude product [3].

Although most synthetic drugs are prepared according to basic well-known methods, the recipes are modified depending on the equipment in the clandestine laboratory and on the chemist. This influences the impurities in the final product. Impurity profiles of drugs from the same source are relatively stable and characteristic whereas the profiles of samples from different sources differ significantly. As a consequence, it is possible to classify samples into groups connected with the clandestine laboratory or with the chemist. The synthetic conditions are relatively easy to control and repeat, therefore the impurity profiles of samples from different batches are similar. Analysis of information connected with the source allows the activity of the laboratory to be assessed.

The most common methods of MDMA synthesis are: reductive amination, Leuckart method, and safrole bromination. The reductive amination of PMK (piperonylmethylketone, 3,4-methylenedioxyphenyl-2-propanone) by methylamine is the most popular method of MDMA synthesis. An imine formed as a result of the reaction is reduced to MDMA by different reducing agents, for example Al(Hg), $NaBH_4$, or $NaCNBH_3$ [7–11]. This method does not require advanced chemical knowledge, equipment, or glassware, is easy to perform, and is characterized by high efficiency. Moreover, the precursors used are easy available.

The other popular method of MDMA production in clandestine laboratories is the Leuckart method. It consists in condensation of PMK with *N*-methylformamide. *N*-formyl-MDMA is formed as a by-product of the reaction and is hydrolysed into MDMA in the presence of hydrochloric acid. Another version of this method is the reaction of PMK with formamide, which leads into formation of *N*-formyl-MDA. This is then reduced into MDMA [10, 12].

The reaction of safrole with hydrobromic acid leads to formation of bromosafrole, which reacts at high temperature and pressure with methylamine forming MDMA [4, 9]. Although the synthesis is not difficult to perform, it requires the advanced equipment and the use of hydrobromic acid, which is very toxic.

Drug profiling aims at determination the similarity of the composition of a sample with that of samples seized in the past and collected in the database. The similarity is assessed by comparison of impurity profiles. The profiles are compared visually or by means of statistical methods using statistical software. Knowledge of the production process, especially the formation and stability of impurities, of the impurities characteristic of the synthetic route (markers), and of possible changes in impurity profiles enables the correct conclusions to be drawn about similarities and differences between samples. Such information can be achieved by detailed chemical analysis of samples from the known sources, when the synthetic route is known.

The most common analytical method used for impurity profiling is gas chromatography, often coupled with mass spectrometry [2, 3, 7, 12, 13]. Other analytical methods are used very rarely, and in a limited range [14–18]. The objective of the study was to assess the possibility of application of high-performance liquid chromatography (HPLC) for profiling of MDMA impurities. In recent years, novel HPLC columns, known as monolithic columns, have become commercially available. Traditionally, the stationary phase in HPLC columns has consisted of tiny silica particles. Monolithic columns, on the other hand, contain a single, solid compound as the stationary phase, which is usually made up of a network of polymethacrylate or polystyrene copolymers, or bonded silica. In particulate columns the mobile phase can diffuse between the particles whereas in monolithic columns it must flow through the solid stationary phase, which is usually porous. Molecules within the mobile phase are then retained to a greater or lesser extent within the pores of the stationary phase or by binding to specific compounds incorporated into the network. Monolithic columns offer a number of advantages over particulate columns, such as faster flow rates and, therefore, quicker separations [19]. The authors decided to assess the abilities of monolithic column in conducting profiling of *ecstasy* tablets.

Material and methods

Chemicals

The following chemicals were used in the studies:

- Solutions (in methanol) of the standards amphetamine, MDA, MDMA, MDEA, ephedrine, ephedrone, 2PEA, PMA, caffeine (1000 μg mL^{-1}) and methamphetamine (100 μg mL^{-1}); Cerilliant, Round Rock, TX, USA;
- Diphenylamine; Sigma–Aldrich, Steinheim, Germany;
- 85% phosphoric acid, chloroform, ethyl acetate, *n*-hexane; POCh, Gliwice, Poland;
- acetonitrile, water, methanol and buffer solution I (pH 7), ready for use, pH 7.00±0.02 (20°C) (phosphate); Merck, Darmstadt, Germany;

– buffer solution II (pH 8.5), prepared in house: 3.85 g CH_3COONH_4 was dissolved in 450 mL water and concentrated ammonia solution was instilled until the appropriate pH was reached;
– buffer solution III (pH 10), prepared in house: 10.7 mL 0.1 mol L^{-1} NaOH, 50 mL of 0.05 mol L^{-1} $NaHCO_3$, and 39.3 mL water were mixed. The chemicals used for preparation of buffer solutions II and III were purchased from POCH.

Material

The material for the studies were MDMA samples prepared in the laboratory by means of Leuckart method and reductive amination using different reducing agents. Details of the synthetic methods are given in the *Introduction*. The reactions were carried out at the Faculty of Chemistry, Jagiellonian University, Krakow, Poland.

Equipment

Impurities were extracted with a Baker spe-12G system with a KNF Laboport vacuum pump. The system enables simultaneous extraction of up to 10 samples. Analysis of the isolated impurities was carried out on La Chrom D-7200 System (Merck–Hitachi) liquid chromatograph equipped with an L-7455 diode-array detector (DAD). A D-7200 autosampler enabled automatic sampling and injection of samples, resulting in excellent repeatability of injections. Compounds were separated on a Chromolith Performance RP-18e monolithic column (100×4.6 mm, 2 μm).

Statistical analysis

Basic calculations were done in Excel. Chemometric analysis was performed by use of "Statistica 5.0" (StatSoft, Tulsa, USA).

Results and discussion

Extraction of MDMA impurities

Selection of the buffer used to dissolve the samples and the volume of eluent used to elute the impurities were the steps of optimisation of the extraction method. Then the repeatability of the method was verified and the extraction efficiency was calculated by the use of diphenylamine as internal standard. All calculations were done on the basis of its peak area.

In order to optimise the extraction of the impurities, a mixture of 1.5 mL of an appropriate buffer (pH 7, 8.5 or 10) and 0.5 mL diphenylamine (0.03 g L^{-1} aqueous solution) was poured on to 5 μg MDMA. This mixture was vortex mixed for 25 min at 2000 rpm using an IKA-Werke Vibrax VXR shaker, then centrifuged at 4600 rpm, and the supernatant was extracted with Bakerbond spe columns filled with octadecylsiloxane phase (C_{18}; 3 mL, 500 mg). Before introduction of the supernatant the extraction column was conditioned with 1.5 mL of the buffer then *n*-hexane, chloroform, ethyl acetate, and methanol, in amounts corresponding to one volume of the column, then with two column volumes of distilled water. Supernatant (0.5 mL) was then introduced to the column at a flow rate of 0.5–1 mL min^{-1}. The columns were then washed with water (3×2 mL) and dried for 5 min under vacuum. The analytes were eluted with methanol (5× 300 μL; each 300-μL portion being collected separately). The samples were prepared for HPLC analysis by addition of 300 μL aqueous phosphoric acid (100 μL L^{-1}).

Chromatographic separation of a sample dissolved in different buffers is shown in Fig. 1.

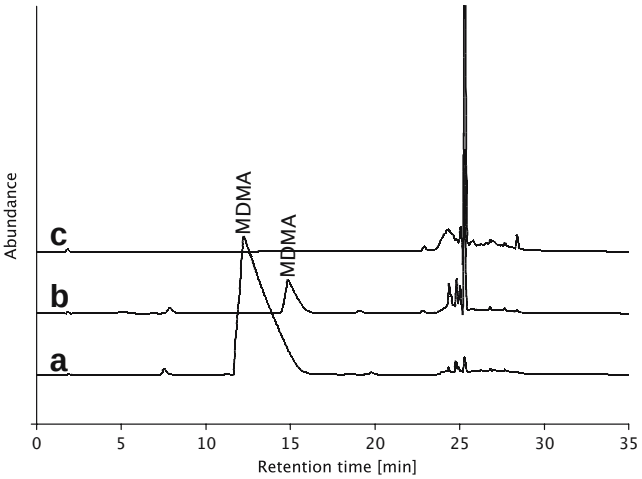

Fig. 1 Comparison of the chromatograms obtained from samples prepared by dissolution in different buffers (different pH): (**a**) pH 10, (**b**) pH 8.5, (**c**) pH 7

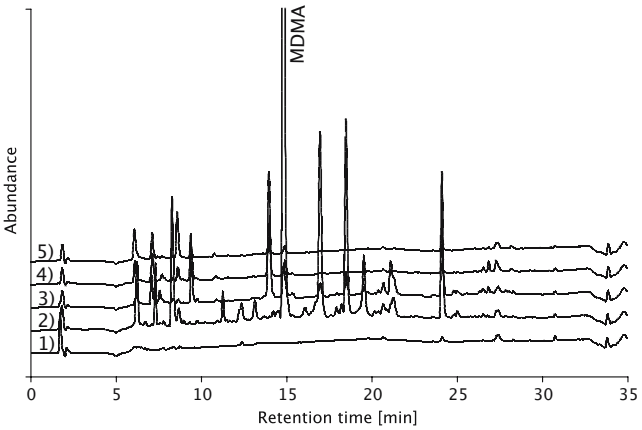

Fig. 2 Chromatograms obtained from the impurities eluted by consecutive 300-μL portions of methanol

Table 1 The starting point of optimisation of the gradient program of mobile phase composition

Time	Amount of water (% *v*/*v*)	Amount of acetonitrile (% *v*/*v*)
0	100	0
20	50	50
30	0	100
31	100	0
35	100	0

Analysis of the chromatograms obtained revealed the best results were achieved by use of buffer of pH 8.5. When buffer of pH 10 was used an extremely large peak was obtained from MDMA, which could lead to its overlapping with peaks from impurities. With buffer of pH 7 an MDMA peak was not observed. Most of the impurities, similar to MDMA, are amines. It is highly probable they are not detected when a solvent of such low pH is used. Analysis of the chromatogram obtained from the sample dissolved in the buffer of pH 8.5 reveals the MDMA peak is present but its area is lower in comparison with the sample extracted at pH 10, with the result that substances with similar properties should be detected.

The chromatograms of the impurities eluted with consecutive portions of methanol are shown in Fig. 2. When the chromatograms were studied it was observed that the first 300-μL portion of methanol did not elute the impurities. The largest number of impurities was detected in the three middle portions of methanol. Finally, the following procedure was used. After adsorption of the impurities on the column and rinsing with water, the first 300-μL fraction of methanol was not collected. Then the impurities were eluted with 900 μL methanol. This enabled reduction of the sample volume from 1500 to 900 μL. The extraction efficiency was 75% for diphenylamine.

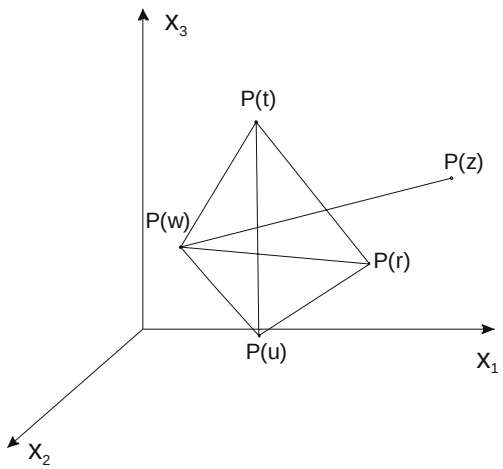

Fig. 3 The simplex in three-dimensional space. The starting simplex is defined by the vertices ($P^{(w)}$, $P^{(t)}$, $P^{(r)}$, and $P^{(u)}$). The vertex $P^{(z)}$ of the ($P^{(z)}$, $P^{(t)}$, $P^{(r)}$, $P^{(u)}$) simplex was obtained by symmetrical reflection of point $P^{(w)}$ in the centre of gravity of vertices $P^{(t)}$, $P^{(r)}$ and $P^{(u)}$

Table 2 The coordinates of the starting simplex expressed by "coded" variables

Vertex	Factor				
	$\widetilde{x}_1$	$\widetilde{x}_2$	$\widetilde{x}_3$	$\widetilde{x}_4$	$\widetilde{x}_5$
1	0	0	0	0	...
2	1	0	0	0	...
3	0.5	0.866	0	0	...
4	0.5	0.289	0.817	0	...
5	0.5	0.289	0.204	0.791	...
...	...	...	...	...	...

The conditions used for HPLC analysis

The impurities were separated by reversed-phase chromatography with gradient elution. Water with addition of 100 μL 85% phosphoric acid per litre and acetonitrile were the eluents. The flow rate was 1 mL min^{-1}. Spectra were collected in the range 200 to 400 nm, and the wavelength monitored was 205 nm. The column was thermostatted at 30°C. The conditions used for chromatographic analyses were controlled by addition of an internal standard (diphenylamine) to each sample.

The simplex method was used for optimisation of the chromatographic separation. This method was developed in the nineteen-seventies [20] and is still widely used to optimise the conditions for HPLC analysis [21–26]. It is also used in the analysis of complex samples by means of other analytical methods [27–30]. The objective of the method was the best separation of the peaks on the chromatograms of MDMA impurities. Visual assessment

Table 3 The coordinates of the vertices of the simplexes for the optimisation of chromatographic separation by means of HPLC method

Vertex	x_1	x_2	x_3	x_4
1	2.5	20	5	10
2	3	20	5	8
3	2.8	22.6	5	7.3
4	2.8	20.9	5.4	7.7
5	2.3	22.3	5.3	9.2
6	2.0	23.5	5.4	9.8
7	2.5	22.4	4.8	9.2
8	2.1	20.5	5.0	11.4
9	2.1	23.5	5.0	10.1
10	1.9	21.8	5.4	10.9
11	1.8	21.5	5.0	12.3
12	2.0	19.0	5.3	11.7
13	1.9	21.3	5.1	11.7

Table 4 The optimised gradient program of mobile phase composition

Time	Phase A (% *v*/*v*)	Phase B (% *v*/*v*)
0	100	0
21.3	59.5	40.5
33.0	0	100
34	100	0
35	100	0

of the chromatograms was the criterion for optimisation. A starting point of optimisation ($P^{(1)}$) were the conditions shown in Table 1.

Taking into account that the eluent strength of the aqueous solution of phosphoric acid in the reversed-phase system is very low, it was assumed that only first two changes of eluent composition and their duration affected the chromatographic separation. The following factors were established:

$x_1 = \frac{dA_1}{dt_1}$ – the velocity changes in the CH_3CN content of the mobile phase in the first step;

$x_2 = t_1$ – time of the first step;

$x_3 = \frac{dA_2}{dt_2}$ – the velocity changes in the CH_3CN content of the mobile phase in the second step;

$x_4 = t_2$ – time of the second step.

In the carried-out process of optimisation by means of the simplex method, the values of the mentioned factors were changed in order to obtain the best separation of MDMA impurities.

Assuming the boundary of the mobile phase composition in both steps as 100% of acetonitrile, the following equation was established:

$$x_1 \cdot x_2 + x_3 \cdot x_4 = 100 \quad (1)$$

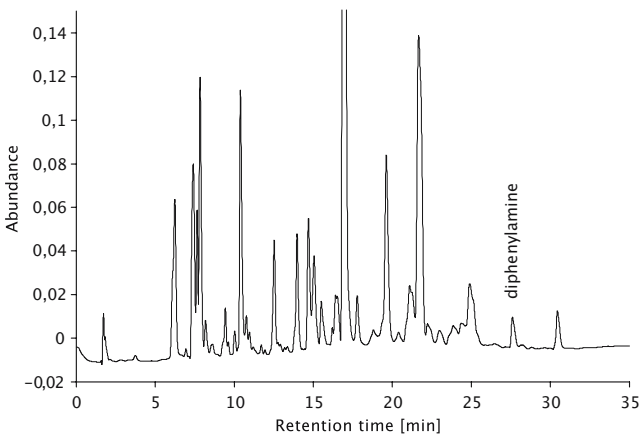

Fig. 4 The impurity profile of the MDMA sample prepared by reductive amination using $NaBH_3CN$ (crude product)

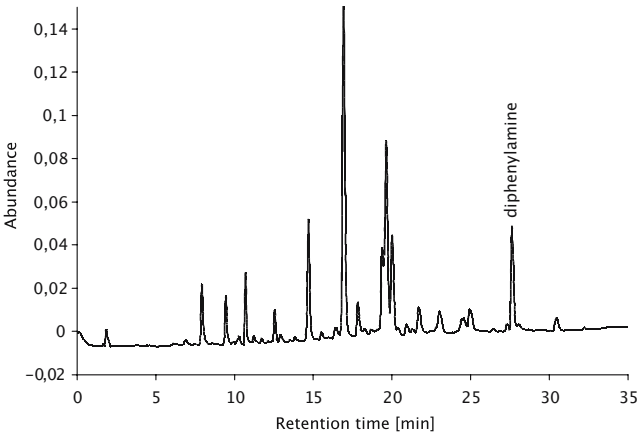

Fig. 5 The impurity profile of the MDMA sample prepared by reductive amination using Al/Hg (crude product)

The time of the second step was calculated as the dependent variable from the following equation:

$$x_4 = \frac{100 - x_1 \cdot x_2}{x_3} \quad (2)$$

The simplex was defined by four points which were its vertices in three-dimensional factor space x_1; x_2; x_3 (Fig. 3).

The coordinates of the staring point of the optimisation ($P^{(1)}$), used for calculation of the vertices in the starting simplex (no 1), were as follows:

$x_1 = 2.5$
$x_2 = 20$
$x_3 = 5$
$x_4 = \frac{100-2.5 \cdot 20}{5} = 10$

The values were calculated on the basis of data from Table 1. The steps Δx_i, which determine the dimensions of the starting simplex and, therefore, the changes of the

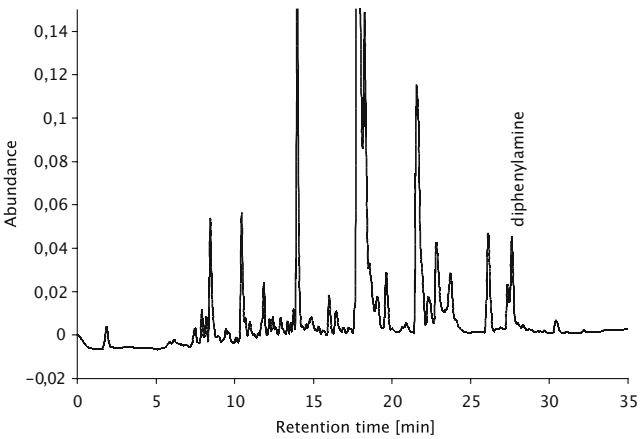

Fig. 6 The impurity profile of the MDMA sample prepared by the Leuckart method with use of diethyl ether (final product after distillation)

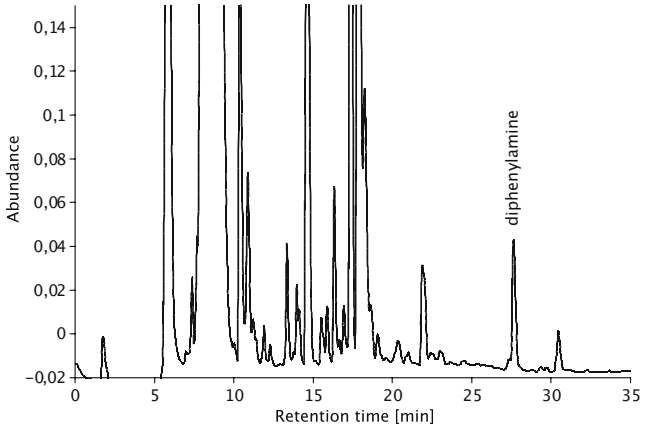

Fig. 7 The impurity profile of the MDMA sample prepared by the Leuckart method with use of *iso*-propanol (final product after distillation)

values of x_i factors in the first optimisation step, were as follows:

$\Delta x_1 = 0.5$
$\Delta x_2 = 3$
$\Delta x_3 = 0.5$

The coordinates x_1, x_2, x_3 of the next j vertices of the starting simplex were calculated from the formula:

$$x_i^{(j)} = x_i^{(1)} + \tilde{x}_i^{(j)} \cdot \Delta x_i \quad (3)$$

where: $\tilde{x}_i^{(j)}$ denotes the "code" variable, which is an element of Table 2 lying at the intersection of column i with row j. The x_4 coordinate was calculated from Eq. (2).

In each of the vertices $P^{(1)}$, $P^{(2)}$, $P^{(3)}$, $P^{(4)}$ of the starting simplex, the chromatographic separation was performed. The gradient program for the mobile phase was adapted to the calculated values. The chromatograms obtained were then compared visually and the worst was selected. The point $P^{(w)}$, corresponding to the worst separation, was reflected in the centre of gravity of the remaining vertices of the simplex (Fig. 3). The coordinates of new point, $P^{(z)}$, obtained as the result of the reflection, were calculated from the formula [20]:

$$x_i^{(z)} = (1-\alpha) \cdot x_i^{(w)} + \frac{\alpha}{n} \sum_{i \neq w} x_i^{(j)} \quad (4)$$

where: $x_i^{(z)}$ denotes the i-th coordinate of the point $P^{(z)}$, $x_i^{(w)}$ the i-th coordinate of the worst vertex $P^{(w)}$, the sum covers the vertices of the simplex except point $P^{(w)}$, $x_i^{(j)}$ denotes the i-th coordinate of these vertices, $\alpha = \frac{|P^{(z)}P^{(w)}|}{|P^{(s)}P^{(w)}|}$ is the ratio of the distances between the points in the simplex, and n is the number of factors.

The point $P^{(z)}$, obtained as the result of the reflection, forms a new simplex with the points $P^{i \neq w}$.

The route of the optimisation of the HPLC separation of MDMA impurities was described by the coordinates x_1, x_2, x_3, x_4 of consecutive simplexes, which are shown in Table 3.

Finally, it was decided that the point $P^{(13)}$, which was the centre of gravity of the points $P^{(8)}$; $P^{(10)}$; and $P^{(11)}$, was the final point of optimisation and the values corresponding to its coordinates were taken as the optimum. The optimised gradient program of mobile phase composition is shown in Table 4.

Impurity profiles

Selected chromatograms of impurities from MDMA samples prepared by different synthetic routes are shown below (Figs. 4, 5, 6, 7).

One of the aims of profiling is to find links between MDMA samples and to allocate the samples to similarity groups (clusters) which cover samples prepared by the same way. Comparison of the profiles obtained (chromatograms) was done by using peak areas of the selected

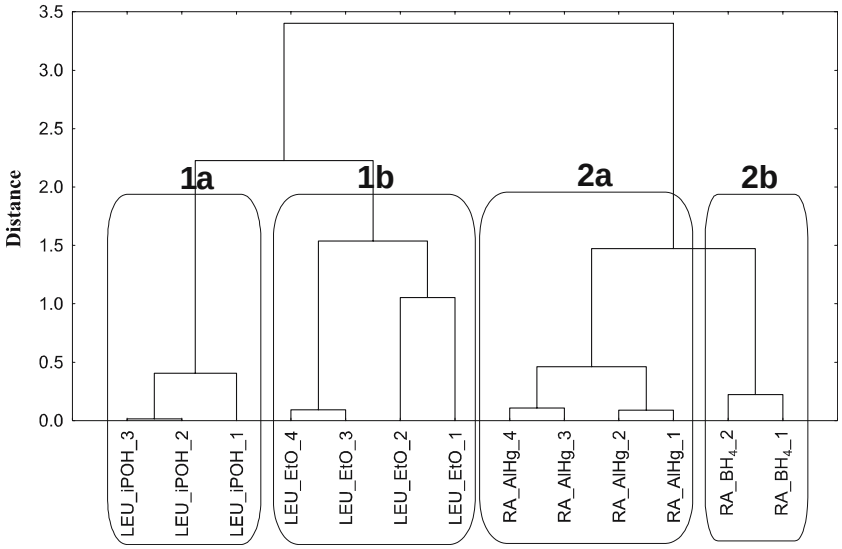

Fig. 8 The dendrogram of MDMA samples. The distance was calculated using the Pearson correlation coefficient. The Ward method was used for agglomeration. The samples are described in Table 5

Table 5 The classification of samples by cluster analysis

Sample name	Synthetic route	Precipitation solvent[a]	Reducing agent	Cluster number
LEU_iPOH_1	Leuckart	*iso*-Propanol	–	1a
LEU_iPOH_2	Leuckart	*iso*-Propanol	–	1a
LEU_iPOH_3	Leuckart	*iso*-Propanol	–	1a
LEU_EtO_1	Leuckart	Diethyl ether	–	1b
LEU_EtO_2	Leuckart	Diethyl ether	–	1b
LEU_EtO_3	Leuckart	Diethyl ether	–	1b
LEU_EtO_4	Leuckart	Diethyl ether	–	1b
RA_AlHg_1	Reductive amination	–	Al/Hg	2a
RA_AlHg_2	Reductive amination	–	Al/Hg	2a
RA_AlHg_3	Reductive amination	–	Al/Hg	2a
RA_AlHg_4	Reductive amination	–	Al/Hg	2a
RA_BH_4_1	Reductive amination	–	BH_4	2b
RA_BH_4_2	Reductive amination	–	BH_4	2b

[a] The substance used to dissolve MDMA (in the basic form) before precipitation of MDMA·HCl by use of hydrochloric acid

impurities, which are characteristic of the appropriate synthetic route. The selected impurities should be as specific for the route as possible and the areas of their peaks should change with changing synthetic conditions. The method of sample comparison and grouping devised was based on the areas of 33 selected peaks corresponding to MDMA impurities. Some of these peaks are characteristic of one synthetic route only ("markers") whereas others can be present in samples prepared by different synthetic routes. The impurities were not identified, because most have very similar UV–visible spectra. The relative retention (separation factor) was calculated for each peak by comparison with the retention time of the internal standard (diphenylamine) and used for identification of the peaks.

Cluster analysis (CA) was used to group the examined samples. It is aimed at grouping samples with similar properties. Intra and inter-group similarity was compared. In our case, the objects were 13 profiles (chromatograms) of MDMA impurities obtained by two different routes. The Pearson correlation coefficient was used for calculation of the distance between chromatograms. The Ward method was applied for agglomeration of clusters. In this method, analysis of variance is used to estimate the distance between groups (clusters) and is aimed at minimising of the sum of squares of the distance between any two clusters, which could be formed in each step. The result obtained from cluster analysis is shown in Fig. 8.

It is apparent from Fig. 8 the samples examined can be divided into four clusters corresponding to the synthetic routes. The first two clusters-1a and 1b-include samples prepared by the Leuckart method whereas the two remaining clusters-2a and 2b-include the samples prepared by reductive amination. The details of sample classification are shown in Table 5.

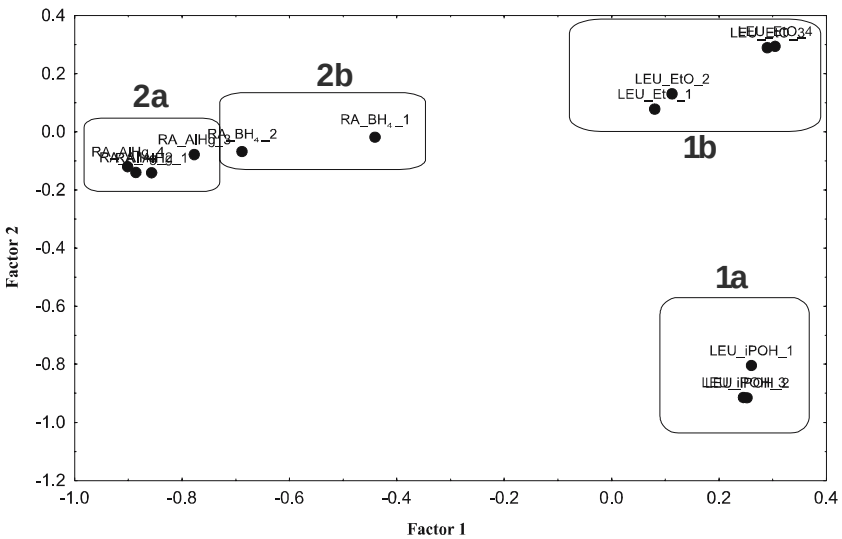

Fig. 9 The result of PCA analysis

In order to verify the clustering of samples by means of CA, principal component analysis (PCA) was applied. The results are shown in Fig. 9.

The results from PCA confirm the results from cluster analysis. Two groups corresponding to different synthetic routes are readily distinguished. This method, similarly to CA, also enables discrimination of samples precipitated from different solvents in the Leuckart method (1a vs 1b) and prepared using different reducing agents (2a vs 2b).

The results from this study show that the qualitative and quantitative composition of MDMA impurities is characteristic of the synthetic method and its conditions. The samples obtained in this series of syntheses, prepared by the same recipe and with use of the same precursors, have very similar compositions of impurities, and changing the synthetic conditions significantly affects the composition of the impurities.

Conclusions

An efficient HPLC method for profiling of MDMA samples was elaborated. A weakly alkaline buffer solution (pH 8.5) enabled extraction of key impurities of MDMA. Solid-phase extraction (SPE) was used to concentrate the impurities and dispose of the relatively large amounts of MDMA hydrochloride. Use of a monolithic column in combination with a mobile phase optimised by use of the simplex method enabled good resolution of the impurities present in MDMA samples.

This method of sample comparison, and grouping on the basis of the areas of 33 selected peaks corresponding to MDMA impurities, gave the correct classification for all the samples tested. They were divided into clusters corresponding to the synthetic route. According to the authors, the strength of this method is comparable with gas chromatography with flame-ionisation detection. When diode-array detection is replaced by mass spectrometry, liquid chromatography can be a supplementary method to GC–MS, or even an alternative method for MDMA profiling.

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