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# Gas chromatographic–mass spectrometric analysis of residual solvent trapped into illicit cocaine exhibits using head-space solid-phase microextraction

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**Abstract**

The analysis of solvent residues trapped into crystals of illicit drugs provides useful evidence for monitoring current use trend in the chemical underground, and is also a suitable tool to achieve the complete chemical characterisation of street drugs for comparative examination of separate specimens. This paper describes a method developed in order to perform simultaneous qualitative and quantitative analysis of solvent residues in cocaine samples. The method is based on GC–MS analysis of solvents after their extraction/concentration from drug matrices accomplished by solid-phase microextraction (SPME) in static head space. The proposed method has been used to detect residues of solvents in 47 illicit street cocaine samples. Quantitative analyses were carried out only for the solvents identified at concentration values higher than 1 ppm. Statistical evaluation of our results allowed us to group the illicit samples into various classes according to different kinds of residual solvent, in connection with different clandestine manufacturing processes used to prepare illicit cocaine. 

*Keywords:* Cocaine

## 1. Introduction

The incorporation of solvents in street cocaine samples is mainly due to the conversion of crude cocaine base to the hydrochloride salt that constitutes the last step during the clandestine production of this drug. In fact, crystallization of the cocaine hydrochloride is generally performed in the presence of the mixture diethyl ether–acetone, but many other steps during the clandestine preparation of cocaine involve the use of solvents that can still be present in the final product [1].

The analysis of solvent residues in illicit cocaine (hydrochloride as well as free base) has been proposed as an aid for both strategic and tactical intelligence. Continuing information on the kind of solvents used during the clandestine preparation of drugs is important to control the availability of these chemicals. Moreover, solvent identification in seized drugs is considered as a suitable tool in comparing different exhibit samples [2–5].

This kind of analysis is mainly performed by head

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space gas chromatography of trace solvent trapped in seized drugs. We suggest a new method based on gas chromatography–mass spectrometry, after solid-phase microextraction of organic solvent achieved by static head space. The proposed method was developed in order to improve the sensitivity and specificity of the analysis.

## 2. Materials and methods

### 2.1. Cocaine samples

Forty-seven illicit cocaine samples, seized over 5 years in the metropolitan area of Rome, were randomly numbered starting from 101 until 147 and were used in this study.

### 2.2. SPME, chemicals and standards

The SPME device was from Supelco (Bellafonte, PA, USA). A 100 μm polymethylsiloxane-coated fibre was used. One-ml microvials were purchased from Hewlett-Packard (Milan, Italy). Solvent standards and other chemicals were from C. Erba Reagenti (Milan, Italy).

### 2.3. Sample preparation

One hundred mg of cocaine samples were added to the microvial together with 100 μl of a saturated solution of sodium chloride in water. The vials were sealed and equilibrated for 5 min at 70 °C. Head space sampling of residual solvent was achieved by SMPE technique for 15 min at the same temperature. After the sampling time the fibre was thermally desorbed directly into the GC injector at 250 °C for 1 min.

Identification of the solvents was performed by retention time and mass spectra.

Calibration curves for quantitative data were prepared adding a known amount of organic solvents to water (when the solvent is soluble in water) or ethylene glycol (when the solvent is not soluble in water). The resulting solutions were diluted and processed as described for the drug samples.

### 2.4. Gas chromatography–mass spectrometry

A Hewlett-Packard gas chromatograph model 5890, equipped with 60 m×0.25 mm I.D. capillary HP1301 column (6% CNPRPH-ME siloxane, 1 μm film thickness) in a temperature program (from 50 to 270 °C) was used. The temperature program was: isothermal mode for 1 min at 50 °C, then 30 °C/min increments to 80 °C, followed by a linear step of 10 °C/min increments until 150 °C, finally 20 °C/min increments to 270 °C hold for 1 min.

The gas chromatograph was coupled with a Hewlett-Packard mass detector model 5889 (electronic impact 70 eV) operating in total ion monitoring (mass range: 29–450 $m/z$).

### 2.5. Statistical evaluation of the results

The chemometrics packages used were UNSCRAMBLER, 1998 (CAMO ASA, Trondheim, Norway) and Statgraphics Plus V 4.0 for Windows, 1994–1999 (Manugistics, Rockville, MD).

A data matrix with rows that are the objects or cocaine samples and with columns that are the variables or solvents was built (47 cocaine samples and 11 variables).

The statistical analysis was performed by means of the UNSCRAMBLER (PCA) and StatGraphics (CA), run on IBM-compatible hardware. The chemometric tools used in this work were as follows.

Data pretreatment: since chemometric tools (e.g. PCA) often work by explaining variation, the variables with maximum variation will be employed in the construction of the model. If the magnitudes of the different variables, e.g. the concentration of solvents within a sample, are often very different, resulting in the higher concentration being more important in the model. This may have the effect of masking the information from the other variables that would have less weight in the model. The data pretreatment used in this study was the half-range central value transformation [6], where the half range, *hr*, and central value, *cv*, are defined as follows

$$hr = x_{\max} - x_{\min}/2$$

$$cv = x_{\max} + x_{\min}/2$$

where $x_{max}$ and $x_{min}$ are the maximum and the minimum concentration for each variable, respectively. Then, all the variables, $x_i$ can be transformed according to

$$z_i = x_i - cv/hr$$

into values of standardised variables, $z_i$. This transformation converts the minimum values to $-1$, the maximum values to $+1$, keeping the average values to 0. This is of great use in pattern recognition because it enhances the differences in the data, and this transformation has been successfully applied for tea sample classification [7].

PCA is a projection method that helps to visualise all the information and it was to achieve a reduction of dimension, i.e. to fit a $K$-dimensional subspace to the original $p$-variate ($p > K$) objects and to observe a primary evaluation of the between-class similarity.

CA is an unsupervised classification procedure that involves a measurement of the similarity between objects to be clustered. Cluster analysis procedure allows you to group observations from a multivariate data set into a cluster of ''similar'' points. By similar, we mean that the observations would be close to each other if they could be plotted in a multidimensional space. The measurement of the similarity is based on the squared Euclidean distance. The clustering method used was Ward's method, which is a hierarchical method. If you have $n$ data points, this method begins with $n$ clusters and reduces the number one at a time by joining each observation or cluster to another cluster. You specify the number of clusters desired in the final result [8].

## 3. Results and discussion

The outlined method, which can easily run in automatic mode, allows the identification and quantification of solvent residues in cocaine samples with high specificity and sensitivity.

We tested 47 cocaine exhibits identifying a total of 32 different volatile organic compounds; among these, the more significant are shown in Table 1 with their retention time values, according to our chromatographic conditions.

The majority of the identified volatile compounds can be related to the manufacturing process. Quantitative data concerning volatile compounds found at levels higher than 1 ppm are listed in Table 2. The letters A, B, C etc. in this table are used to indicate the various solvents found in the cocaine samples, as referred to in the footnote of Table 2.

Table 1
Volatile organic compounds identified in 47 illicit cocaine samples, listed according to their absolute retention time (gas chromatographic conditions are referred to in the text)

| Retention time (min) | Solvent names |
|---|---|
| 4.30 | Methanol |
| 4.60 | Ethanol |
| 4.76 | Pentane |
| 4.80 | Diethyl ether |
| 4.96 | 2-Propanol |
| 5.10 | Acetone |
| 5.20 | Methyl pentane |
| 5.30 | Dichloromethane |
| 5.60 | Hexane |
| 6.00 | 2-Butanone |
| 6.02 | Methyl cyclopentane |
| 6.04 | Ethyl acetate |
| 6.30 | Chloroform |
| 6.50 | Cyclohexane |
| 6.60 | Acetic acid methyl ester |
| 6.70 | Benzene |
| 7.40 | *n*-Propyl acetate |
| 7.50 | Methyl cyclohexane |
| 8.00 | Methyl isobutyl ketone |
| 8.30 | Toluene |
| 9.90 | Ethyl benzene |
| 10.40 | 1,3-Dimethyl benzene |
| 10.70 | 2-Butoxyethanol |
| 11.40 | Decane |
| 11.50 | 1,2,3-Trimethyl benzene |
| 12.70 | Undecane |
| 12.88 | Acetophenone |
| 13.20 | 2-Butoxy ethylacetate |

Typical GC–MS chromatograms reconstructed on the total ion current of two separate exhibits of cocaine hydrochloride with different residual solvents are reported in Figs. 1 and 2.

The mixture diethyl ether–acetone is mainly used during the crystallization step [1]; this kind of solvent should be frequently observed in cocaine hydrochloride. However, our data show that in addition to diethyl ether and acetone ethyl and propylacetate, 2-butanone, methyl chloride and aromatic hydrocarbons, alone or in combination were detected in cocaine hydrochloride exhibits. This is

Table 2
Quantitative data (ppm) for volatile compounds found in 47 illicit cocaine samples at concentration values higher than 1 ppm

| Sample no. | Solvent amount (ppm) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I | J | K |
| 101 | 74 | | | 177 | 680 | | 83 | 450 | 136 | 46 | |
| 102 | | | | | 6740 | | 480 | | | 540 | |
| 103 | | | | 108 | 3140 | | 3 | | | 28 | |
| 104 | 285 | | | 840 | | 2550 | 15 | 160 | | 27 | 230 |
| 105 | | 700 | 1260 | | | | | | | | |
| 106 | 310 | | | | | 1740 | 32 | 380 | 260 | 146 | 340 |
| 107 | 240 | | | | 6080 | | 260 | | 18 | 380 | |
| 108 | | | | 1500 | 4000 | | 28 | | | 21 | |
| 109 | | 92 | 920 | | | | | | | | |
| 110 | | 68 | 433 | | | | | | | | |
| 111 | | 150 | 210 | | | | | | | | |
| 112 | | | | 1320 | 2620 | | 30 | | | 32 | |
| 113 | | | | 1560 | 1930 | | 55 | | | 54 | |
| 114 | | | 1500 | | | | | | | | |
| 115 | | | | 160 | | 1790 | 10 | 150 | | | |
| 116 | 140 | | | | | 1160 | 25 | 1140 | 210 | 98 | 63 |
| 117 | 198 | | | | | 3310 | | 10 | 70 | 30 | 25 |
| 118 | | | | 1320 | 2300 | | 224 | | | 190 | |
| 119 | | | | | 1290 | | 6 | | | 16 | |
| 120 | | 890 | 1460 | | | | 1 | | | | |
| 121 | 240 | | | 1680 | | 1530 | 16 | 960 | 320 | 100 | 450 |
| 122 | | 450 | 1030 | | | | 1 | | | 75 | |
| 123 | | | | 2250 | 2980 | | 103 | | | 104 | |
| 124 | | | | 1270 | 2580 | | 75 | | | 300 | |
| 125 | 18 | | | | | 2740 | 15 | 10 | 64 | 156 | 120 |
| 126 | 499 | | | | | 4000 | 1 | | | 350 | 94 |
| 127 | | | | | 5260 | | 400 | | | 1640 | |
| 128 | | | | 790 | 3400 | | 54 | | | 65 | |
| 129 | 187 | | | | | 2750 | 36 | 880 | 520 | 230 | |
| 130 | | 96 | 476 | | | | | | | | |
| 131 | | 280 | 500 | | | | | | | | |
| 132 | | | | 3320 | 5850 | | 320 | | | 310 | |
| 133 | | | | | 1800 | | 140 | | 50 | 200 | |
| 134 | | 176 | 526 | | | | | | | | |
| 135 | 23 | | | | | 240 | 63 | 1160 | 340 | 65 | |
| 136 | 195 | | | | | 1740 | 7 | | 240 | 104 | 390 |
| 137 | 495 | | | | 3310 | | 5 | | 41 | 83 | 59 |
| 138 | | | | | 5620 | | 11 | | | 35 | |
| 139 | | 232 | 712 | 103 | | | | | | | |
| 140 | 100 | | | 460 | | 237 | 26 | 190 | 12 | 330 | |
| 141 | 195 | | | 2020 | | 2500 | 23 | 24 | 3 | 280 | 100 |
| 142 | 27 | | | | | 3140 | 9 | 240 | 188 | 540 | |
| 143 | | | | | 1940 | | 62 | 1070 | | 250 | |
| 144 | 82 | | | | 2950 | | 24 | 246 | 150 | 270 | |
| 145 | 300 | | | 550 | | 2860 | 40 | 1390 | 76 | 320 | |
| 146 | | | | | 980 | | 24 | 380 | 100 | 100 | |
| 147 | | | | 1570 | 2330 | | 110 | | | 210 | |

Solvent symbols: A, 2 propanol; B, diethyl ether; C, acetone; D, dichloromethane; E, 2-butanone; F, ethyl acetate; G, benzene; H, *n*-propyl acetate; I, isobutyl methyl ketone; J, toluene; K, 2-propyl acetate.

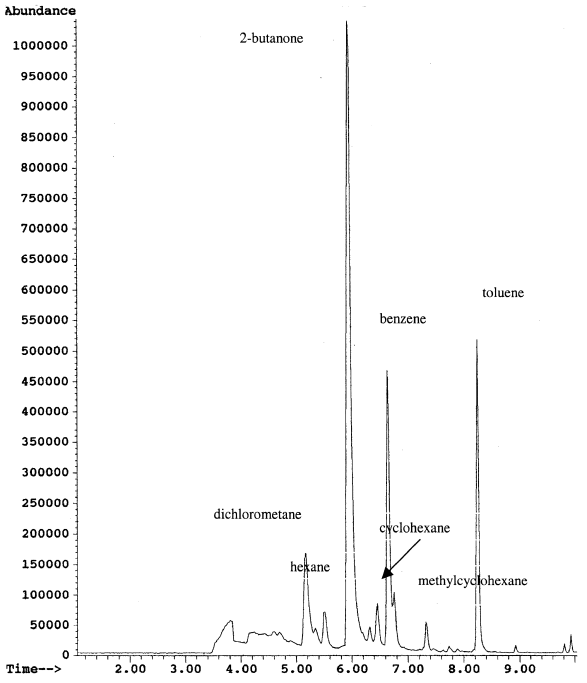


Fig. 1. GC–MS chromatogram of sample no. 128.

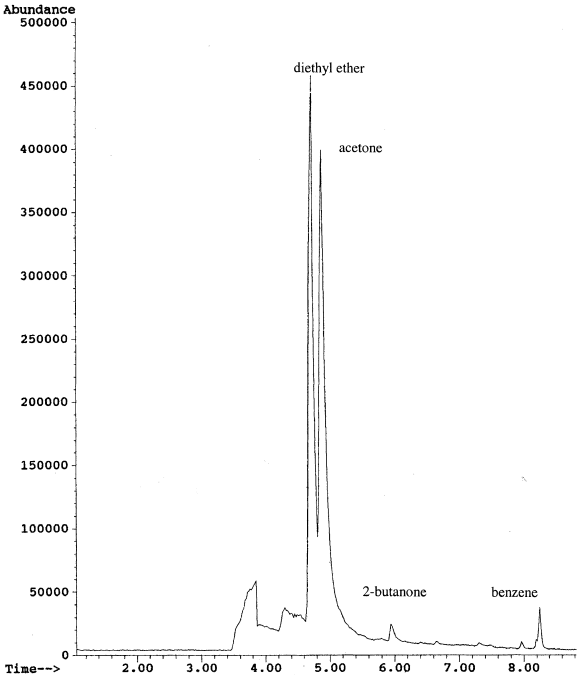


Fig. 2. GC–MS chromatogram of sample no. 131.

probably related to the frequent use of different kinds of solvents during the crystallization of hydrochloride, as demonstrated by the relative low number (10 cases) of positive identifications for diethyl ether and acetone found on 47 samples analyzed.

Residual solvents were found also in old cocaine samples, seized 5 years before and stored at room temperature in glass tubes sealed with silicon rubber. This fact confirms the sufficient stability of solvents trapped into the drug crystals [2–5] that allows to perform this kind of analysis also on old samples. In this connection, the dissolution of drug crystals in water before head space sampling can be considered as an aid for the detection of solvents trapped inside the crystals. Studies are in progress to evaluate the effects of different storing conditions on the quantitative amount of residual solvents.

In order to investigate the reliability of solvent analysis in comparative examination of cocaine exhibits, we carried out a statistical evaluation of our data with the aim to group the exhibits in different classes, according to their residual solvent contents. It is evident that this comparative examination cannot be carried out with conventional univariate techniques because a certain class or group of cocaine samples is related with overall solvent concentrations rather than one by one. Therefore, the use of multivariate statistical methods is necessary to find out the relationship between cocaine exhibits. In addition, multivariate statistical techniques take the overall solvent concentrations and the interaction between solvents is taken into account to establish the relationship.

A principal component analysis (PCA) model was carried out using the cross-validation as validation method. All 47 cocaine samples and 11 solvents (as reported in Table 2 and named A, B, C, etc.) were used in the study. The three first principal components represented 89% of the total variability. Table 3 lists the weights of the 11 variables (solvents) in the first three principal components as well as the equations for the first three principal components. It can be seen that the contents of 2-propyl acetate (K), toluene (J), diethyl ether (B) and isobutyl methyl ketone (I) in cocaine are the dominating features in the first principal component, that accounts for 73% of the total variability. However, the weights of the remaining variables (sol-

Table 3
Weights of solvents (variables) in the first three principal components

| Solvent name and solvent symbol (in brackets) | First principal component | Second principal component | Third principal component |
|---|---|---|---|
| 2-Propanol (A) | 0.296 | −0.294 | −0.167 |
| Diethylether (B) | 0.332 | 0.130 | 0.495 |
| Acetone (C) | 0.284 | 0.144 | 0.703 |
| Dichloromethane (D) | 0.293 | 0.208 | −0.149 |
| 2-Butanone (E) | 0.224 | 0.551 | −0.351 |
| Ethyl-acetate (F) | 0.272 | −0.466 | −0.143 |
| Benzene (G) | 0.304 | 0.369 | −0.209 |
| *n*-Propyl-acetate (H) | 0.306 | −0.248 | −0.078 |
| IBMK (I) | 0.321 | −0.223 | −0.051 |
| Toluene (J) | 0.323 | 0.155 | −0.113 |
| 2-Propyl-acetate (K) | 0.344 | −0.201 | −0.037 |
| PC1 = 0.296A + 0.332B + 0.284C + 0.293D + 0.224E + 0.272F + 0.304G + 0.306H + 0.321I + 0.323J + 0.344K | | | |
| PC2 = −0.294A + 0.130B + 0.144C + 0.208D + 0.551E − 0.466F + 0.369G − 0.248H − 0.223I + 0.155J − 0.201K | | | |
| PC3 = −0.167A + 0.495B + 0.703C − 0.149D − 0.351E − 0.143F − 0.209G − 0.078H − 0.051I − 0.113J − 0.037K | | | |

vents) are also high (Table 3). As the first principal component represents 73% of the total variability, it must be said that all solvents contribute to the classification at the same extension, and the membership of a certain cocaine sample to a certain category or class is because of the contents of all solvents.

Examining a three-dimensional plot (scores plot shown in Fig. 3) of the cocaine samples in the space defined by the three first principal components

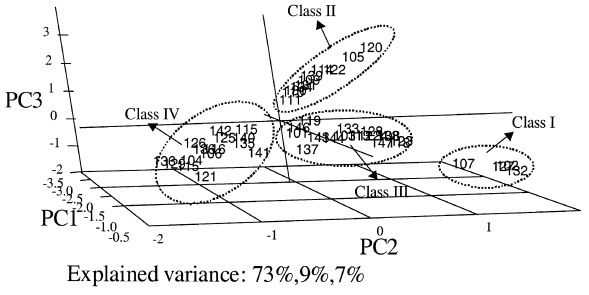


Fig. 3. Scores plot of the cocaine samples in the three-dimensional space formed by the first three principal components.

(linear combination of all solvents according to Table 3) a successful separation between cocaine samples was found and according to PCA results, cocaine samples were grouped in four classes as shown in Table 4.

A cluster analysis (CA) was applied to the data set using the squared Euclidean distance between objects and Ward's method as hierarchical agglomerative procedure. Results are shown as dendrogram plots in Fig. 4 for variables (solvents) and cocaine samples, respectively. From Fig. 4a (at a distance of 200) three main clusters can be seen. As is shown in the legend to Fig. 4a, results obtained after CA agree with those obtained by PCA from which the same group of variables have been observed. In the same way, from Fig. 4b (at a distance of 300) four clusters can be obtained (see legend to Fig. 4b).

Therefore, both principal components analysis (PCA) and cluster analysis (CA) allow the classification of cocaine exhibits in four different classes according to the residual solvent content. The PCA and CA models created are useful to identify new

Table 4
Cocaine sample groups after PCA

| Class number | Cocaine samples |
|---|---|
| I | 102, 107, 127, 132 |
| II | 105, 109, 110, 111, 114, 120, 122, 130, 131, 134, 139 |
| III | 101, 103, 108, 112, 113, 118, 119, 123, 124, 128, 133, 137, 138, 143, 144, 146, 147 |
| IV | 104, 106, 115, 116, 117, 121, 125, 126, 129, 135, 136, 140, 141, 142, 145 |

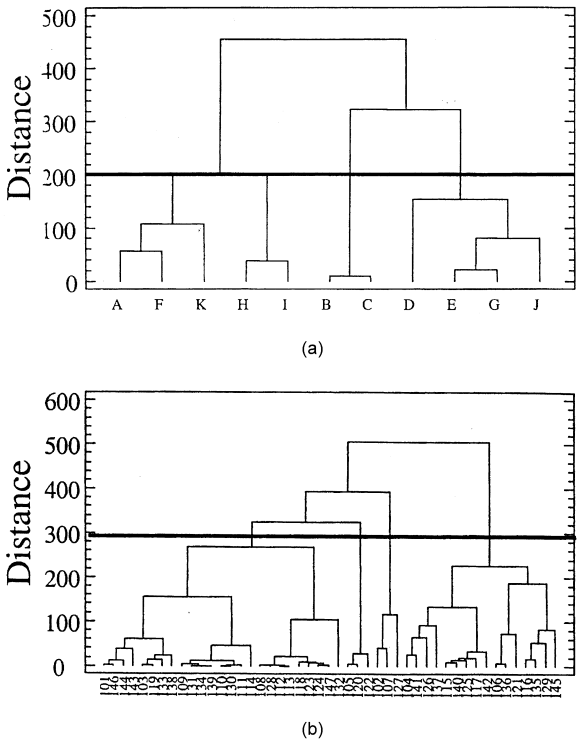


Fig. 4. (a) Dendrogram of cluster analysis for solvents (beginning from left): 1st cluster composed of five solvents: 2-propanol (A), ethyl acetate (F), 2-propyl acetate (K), *n*-propyl acetate (H) and isobutyl methyl ketone (I); 2nd cluster formed by two solvents (diethyl ether (B) and acetone (C)); 3rd cluster of four variables, dichloromethane (D), 2-butanone (E), benzene (G) and toluene (J). (b) Dendrogram of cluster analysis for cocaine hydrochloride samples (beginning from left): 1st cluster is formed by 25 cocaine samples (101, 146, 144, 143, 103, 119, 133, 138, 109, 131, 134, 139, 110, 130, 111, 114, 108, 128, 112, 113, 118, 123, 124, 147 and 132). Most of these samples belong to class III (PCA). Second and third clusters are formed by three samples each: numbers 105, 120, 122 and 102, 107, 127 for the second and the third cluster, respectively. Cocaine samples in the second cluster belong to class II (according to PCA), while cocaine samples in the third cluster belong to class I (PCA). Fourth cluster formed by 16 samples: 104, 141, 126, 137, 115, 140, 125, 117, 142, 106, 136, 121, 116, 135, 129 and 145. All these samples, except cocaine 137, belong to class IV (PCA).

cocaine exhibits after the residual solvent determination. If the new sample belongs to a certain class or cluster, we can say that this cocaine exhibit was obtained (crystallized) using the same procedure as the other cocaine samples that belong to that class.

The proposed analytical method can be used as an additional tool for comparative analyses of illicit drug samples, adding more details about the chemical fingerprint of the samples, as required to compare separate specimens.

The complete chemical characterization of illicit cocaine samples is generally carried out by various analytical methods (TLC, HPLC, CG, GC–MS, etc.) involving the identification of both major and minor components. The analytical procedures used for this purpose are mainly based on quantitative analysis of cocaine content in the street sample (major component) and identification of minor components such as relative amount of *cis* and *trans* cinnamoyl cocaines, truxillines and related compounds, manufacturing by-products (oxidation and hydrolysis products) [9].

In order to evaluate the efficacy of the quantitative solvent analysis, we performed the characterization of cocaine purity and the identification of *cis* and *trans* cinnamoyl cocaines as well as the manufacturing by products (*N*-norcocaine, *N*-formylcocaine, benzoylecgonine) on the samples used through this study on residual solvents. The analyses was carried out by GC–MS (electronic impact 70 eV) after dissolution of the illicit cocaine samples in methanol, according to the procedure usually employed for routine comparison of cocaine, reported elsewhere [9,10].

Many samples that were grouped in the same classes by principal component analysis (PCA) showed similar chemical composition in terms of major and minor components. This confirms the reliability of the quantitative analysis of residual solvents in illicit cocaine. Hence the proposed methods could be successfully used during chemical profiling of cocaine samples to obtain more information on deep chemical composition of separate specimens. Obviously a complete characterization of drug samples compels the detection of a variety of components with different analytical approaches, among these the identification of the pattern of residual solvent can be an aid to perform a valid comparative analysis.

In conclusion, according to literature data [1–5], we can confirm that quantitative profile of the solvents trapped into illicit cocaine can be used as a suitable tool to investigate the kind of solvent involved during the clandestine manufacturing of the drug. This analysis provides evidence of the current

use trend in the chemical underground and in this connection, this study shows that samples recently seized in the metropolitan area of Rome are frequently characterized by a high amount of ethyl acetate, while the presence of diethyl ether–acetone was seldom observed. These compounds, that were considered as more representative residual solvents related to clandestine crystallization process of illicit cocaine [1], were infrequently detected, mainly in old samples.

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