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Development of visual peak selection system based on multi-ISs normalization algorithm to apply to methamphetamine impurity profiling

Hun Joo Lee[a], Eunyoung Han[b,c], Jaesin Lee[d], Heesun Chung[e], Sung-Gi Min[a,*]

[a] Department of Computer Science and Engineering, Korea University, 145, Anam-ro, Seongbuk-gu, Seoul, Republic of Korea
[b] College of Pharmacy, Duksung Women's University, 33, Samyangro 144-gil, Dobong Gu, Seoul, Republic of Korea
[c] Innovative Drug Center, Duksung Women's University, 33, Samyangro 144-gil, Dobong Gu, Seoul, Republic of Korea
[d] National Forensic Service Drug & Forensic Toxicology Division, National Forensic Service 10 Ipchun-ro, Wonju 220-170, Republic of Korea
[e] Graduate School of Analytical Science and Technology, Chungnam National University, Daejeon, Republic of Korea

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ABSTRACT

The aim of this study is to improve resolution of impurity peaks using a newly devised normalization algorithm for multi-internal standards (ISs) and to describe a visual peak selection system (VPSS) for efficient support of impurity profiling. Drug trafficking routes, location of manufacture, or synthetic route can be identified from impurities in seized drugs. In the analysis of impurities, different chromatogram profiles are obtained from gas chromatography and used to examine similarities between drug samples. The data processing method using relative retention time (RRT) calculated by a single internal standard is not preferred when many internal standards are used and many chromatographic peaks present because of the risk of overlapping between peaks and difficulty in classifying impurities. In this study, impurities in methamphetamine (MA) were extracted by liquid–liquid extraction (LLE) method using ethylacetate containing 4 internal standards and analyzed by gas chromatography-flame ionization detection (GC-FID). The newly developed VPSS consists of an input module, a conversion module, and a detection module. The input module imports chromatograms collected from GC and performs preprocessing, which is converted with a normalization algorithm in the conversion module, and finally the detection module detects the impurities in MA samples using a visualized zoning user interface. The normalization algorithm in the conversion module was used to convert the raw data from GC-FID. The VPSS with the built-in normalization algorithm can effectively detect different impurities in samples even in complex matrices and has high resolution keeping the time sequence of chromatographic peaks the same as that of the RRT method. The system can widen a full range of chromatograms so that the peaks of impurities were better aligned for easy separation and classification. The resolution, accuracy, and speed of impurity profiling showed remarkable improvement.

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1. Introduction

Impurity profiling has been used for many purposes, and, in particular, it is required in the crackdown on drug trafficking in the forensic field. Illicit drugs are manufactured in secret and distributed by organized crime groups, thus there are many difficulties involved in the investigation. Impurities in drugs from the environment of the manufacturing location, such as soil or artificially added during synthesis, can be used as a marker for identification of the similarity between seized drugs [1,2]

Drug impurity profiling has been studied in many countries including Asian countries (South Korea [3–7], Philippines [8], and Japan [9–11]), European countries (UK [12], France [13], Switzerland [14,15], Germany [16], and Sweden [17]) [18], USA [2,19–23], and Australia [1,24]. Many researchers have conducted impurity profiling of methamphetamine (MA) [3,4,6–11,25], heroin [17,22,26], cocaine [14,20,24], methylenedioxymethamphetamine (MDMA) [13,21], and cannabinoid [5,16,23] using GC [14].

Two analytical methods have frequently been used in the impurity profiling of MA and amphetamine samples. United Nations Office on Drugs and Crime (UNODC) reported an

* Corresponding author.
E-mail address: adstar2000@empas.com (S.-G. Min).

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analytical method of MA impurity profiling in 2000. MA samples were extracted with ethyl acetate containing three internal standards (ISs). Analysis was then performed by a gas chromatography-flame ionization detector (GC-FID) equipped with an Ultra-2 (HP) column [27]. In 2003, an analytical method defined as the 'National Research Institute of Police Science (NRIPS) method' was suggested by Inoue et al. [10] for use in MA impurity profiling. MA samples were extracted with ethyl acetate containing 4 ISs, the organic layer was injected into a gas chromatography-flame ionization detector (GC-FID). The instrument was equipped with a DB-5 capillary column [10]. The NRIPS methods developed in Japan have been used in many Asian countries including South Korea. It was improved for detection of more impurities and less MA [7].

The gas chromatogram data (RT and peak area) should be evaluated using proper statistical methods for profiling many kinds of impurities in seized drugs. The three statistical indices using distance measures have been frequently used in drug profiling: the Euclidean distance [3,8–11], Canberra's metric similarity coefficient [28,29], and the quotient method [15,17,30,31]. Inoue et al. [10] processed their data using Euclidean distances with the following steps. The relative retention times of each peak were calculated by dividing the RT of the peak by those of the two nearest ISs before and after the peak. Each peak area was corrected by one internal standard (*n*-hexacosane) and Euclidean distances between any two chromatograms were calculated using common logarithms multiplying their relative areas by 1000. Then further classification of samples was performed using Hierarchical cluster analysis [10]. Combination of Euclidean distance and logarithmic conversion of relative area has recently been widely used for impurity profiling of MA [11]. Strömberg et al. [17] used a quotient method to examine the similarity between drug samples. In the software, the quotients of corresponding peaks from each sample were calculated and used to determine similarity between samples. The ratio between the identical peaks in two samples was calculated, and the number of peaks showing similar ratios indicated similarity between two samples.

In this study, the visual peak selection system (VPSS) demonstrated rapid and efficient impurity profiling using a normalization algorithm with enhanced resolution and accuracy.

2. Materials and methods

2.1. Sample collection

Six MA samples (nos.728, 733, 749, 812, 967, 985) were obtained from 6 police stations in Seoul and Gyeonggi-do from 2009 December to 2010 June. Five samples were in the form of white crystals and 1 was light yellow crystals. All samples came from different sources.

2.2. Sample preparation

The methods were described in the previously published papers [7,10,11]. The NRIPS method developed in Japan [10] was used to extract the impurities in MA samples. Extraction buffer was a mixture of 0.1 M phosphate buffer (pH 7.0) and 10% Na_2CO_3 (4:1). MA sample was dissolved in the extraction buffer. The solution was vortexed for 10 min with ethyl acetate including 4 ISs (ndecane, *n*-pentadecane, *n*-eicosane, *n*-octacosane) for extraction. After centrifuging, the organic layer was obtained and 1 uL was injected into a gas chromatography-flame ionization detector [10].

2.3. GC-FID

The gas chromatographic methods from the previously published papers were used [7,10,11]. An Agilent Technologies HP6890N gas chromatograph coupled with a flame ionization detector was used for analysis. HP7683 autosampler and DB-5 capillary column (30 m length × 0.32 mm i.d. × 1.0 mm film thickness) were used. The oven temperature was as follows: 50 °C for 1 min, 10 °C/min to 300 °C, and held for 10 min at 300 °C. Helium was used as a carrier gas (the flow rate was 2 mL/min). Sample was injected in splitless mode.

Table 1
Modules and features of the VPSS.

Phase	Module name	Macro features
I	Input	Import chromatography sample datasets in a lump Add the datasets to a database Preprocessing - Auto-detection of multi-ISs - Remove unnecessary peaks such as Solvent or ISs
II	Conversion	Convert RTs into Corrected RRT (Crrt) dimension
III	Detection	Crrt dimensional rendering for impurities of samples Visual peak selection and detection

2.4. The development environment and sub-module configuration of the VPSS

The system is executed on the operating system of MS-Windows 7 above. The programming language and methodology used C#.NET and object-oriented programming techniques. In particular, a multi-threading technique is applied for efficiency of detecting and rendering many samples and impurities simultaneously. The system consists of 3 sub-modules, shown in Table 1. The input module imports qualitative and quantitative characteristics data from chromatography raw data and manages data systemically after preprocessing and encoding based on the relational database. It is converted with a normalization algorithm in the conversion module, and finally the detection module detects the impurities in MA samples using a visualized zoning user interface.

2.5. Data processing

Data processing was performed according to the following steps: (1) data collection, preprocessing and archive regarding the quantitative and qualitative characteristics of samples and internal standards using an input module. (2) Data converted with conversion modules using the normalization algorithm. (3) Data visualizing, rendering and detection of impurities included in the samples.

3. Results

3.1. Development of a normalization algorithm in the conversion module of VPSS

GC-FID results of 6 MA samples with 4 IS were collected in the form of an Excel file, retention time of the chromatograms were corrected by the average values of ISs and the peak area was then divided by the area of ISs for area normalization. The detailed process was described in the previously published literature [7]. After RRT automatic identification, the chromatographic peaks of solvents, ISs, and MA were removed in order to clarify peaks of impurity (**Preprocessing**). The collected RT and peak area was converted by the normalization algorithm in the conversion module (**Normalization**). Chromatographic peaks were then rendered in order of Crrt (**Peak alignment or Peak rendering**). The final result from the conversion module was used for further similarity assessment of seized MA samples.

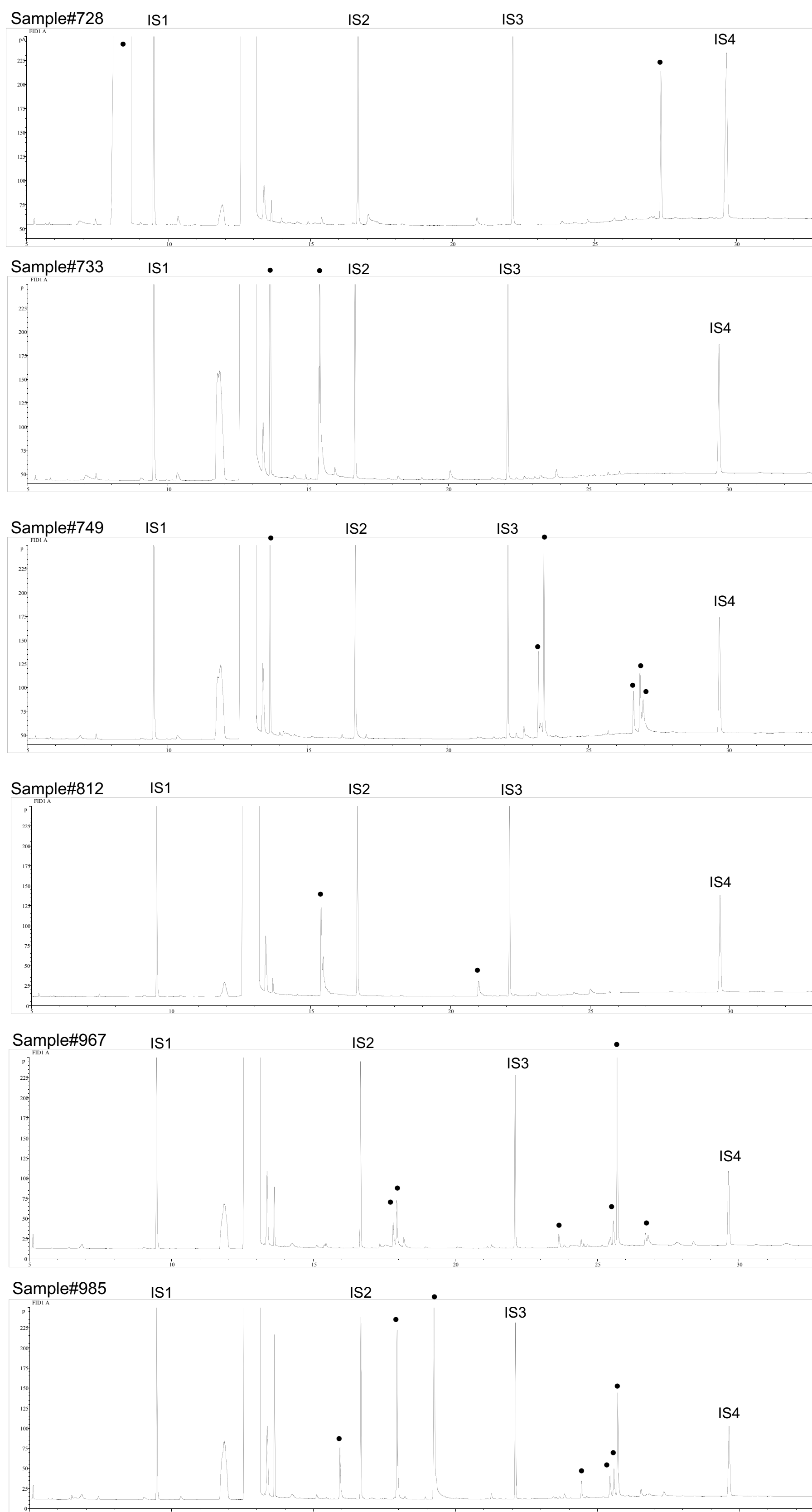

Fig. 1. GC chromatograms of 6 MA samples.
Impurities were detected as peaks marked as a black circle.

Table 2
Comparison of calculation between RRT and Crrt.

	RRT	Converted RRT (Crrt)[a]
Crt(1)	a/b	a/b
Crt(2)	c/e	1 + (c – b)/(e – b)
Crt(2)	d/e	1 + (d – b)/(e – b)
Crt(3)	f/h	2 + (f – e)/(h – e)
Crt(3)	g/h	2 + (g – e)/(h – e)
Crt(4)	i/j	3 + (i – h)/(j – h)
Range of RRT	(0, 1)	(0, 4)

[a] Converted RRT was calculated by normalization and fragmentation.

3.1.1. Normalization algorithm

Fig. 1 shows GC chromatograms of 6 MA samples. Four internal standards were used to correct RT and impurities were detected as peaks marked as a black circle. Because many internal standards were used in the analysis, many chromatograms appeared and relative retention time was not distinct enough for use as a marker because it could be overlapped.

Traditional relative retention time (RRT) of a peak was calculated as follows: the retention time of a peak was divided by the later retention time of the IS peak among the two nearest IS peaks before and after the peak (the left column of Table 2). Table 2 summarizes the calculation rule of RRT and the corresponding chromatogram is shown in Fig. 2. As the number of impurities and ISs in samples increase, RRT tends to converge to 1. The risk of overlap between RRTs increases, resulting in low accuracy and low efficiency of analysis.

To overcome the overlap phenomenon, the normalization algorithm shown below was newly developed for use in the conversion module to convert the retention time data (Eq. (1)).

$$C_{rrt}(i) = (i-1) + \frac{C_{rt}(i) - IS_{rt}(i-1)}{IS_{rt}(i) - IS_{rt}(i-1)} \quad (1)$$

$C_{rrt}(i)$: Crrt of the impurity which is later than (i – 1)th IS and earlier than ith IS on the chromatogram, $C_{rt}(i)$: RT of the impurity which is later than (i – 1)th IS and earlier than ith IS on the chromatogram, $IS_{rt}(i)$: RT of ith IS, i: Order of IS, i > 0 and ISrt (0) = 0.

Table 2 shows the comparison of the RRT (left column) and the **converted relative retention time (Crrt)** (right column) from the normalization algorithm. As shown in the right column of Table 2, the **Crrt** varied from 0 to 4 and the full range was widened depending on the number of ISs so that the peaks were better aligned for easy separation and classification. Crrt is calculated by implying the original sequence of RRT of each peak and classifies each peak according to the sequential area between ISs. The normalization algorithm implies the relative positions between all ISs and all peaks of impurities with relatively high resolution. Fig. 3 shows the converted chromatogram of the representative MA sample, and Crrt varies from 0 to 4 and Fig. 4 shows the distinctly high resolution of 6 MA impurity profiles after application of a normalization algorithm.

3.2. Implemented features of VPSS

VPSS, a computer program that enables supporting the selection of core impurities in multiple samples for impurity profiling in an intuitive way, consists of input, conversion, and detection module. In the input module, users choose single or multiple chromatography data files for impurity profiling. The system extracts and imports qualitative and quantitative data (e.g., peak RT, area, height etc.) and adds the datasets to a database in a lump. During this time, ISs and solvent peak are checked automatically by applying a pre-defined RT value and tolerance and marked as unused peak. The conversion module converts RTs into Crrt dimension space throughout all imported samples. Finally, the detection module, which provides the visual environment for peak selection in the Crrt dimension, loads the impurities data of samples for impurity profiling from the VPSS database by sample. All impurities' RRTs are rendered on the Crrt dimension space and the sample name of each impurity is labeled, shown in Fig. 4. In addition, various options related to rendering are supported, including 2D/3D look and chromatogram style. Users can select the samples (left-top Fig. 4) or a zone (left-bottom Fig. 4). The zone indicates the set of impurities positioned in front of nth IS. Users can select and detect the impurities in the area specified by drag-and-drop of a mouse from RRTs visualized on Crrt dimension space (Fig. 5). In addition, because the system saves all information related to the detected impurities, it provides links to other information (e.g., peak height, area, area ratio etc.) organized with the selected impurity and the various data tables in downloadable spreadsheet format for later statistical analysis.

4. Discussion

Impurities in drugs from the environment of the manufacturing location, such as soil or artificially added during synthesis can be used as a marker to identify similarities between drug samples, synthetic method, and the location of manufacture by analysis of its appearance and quantity. While impurity profiling has enabled a more efficient crackdown on illicit drugs, there is still some limitation in raw data processing in terms of resolution, accuracy, and speed.

4.1. Resolution improvement

The data processing method using relative retention time (RRT) is not a sufficient criterion for classifying impurities when analytical samples contained numerous impurities and ISs. The

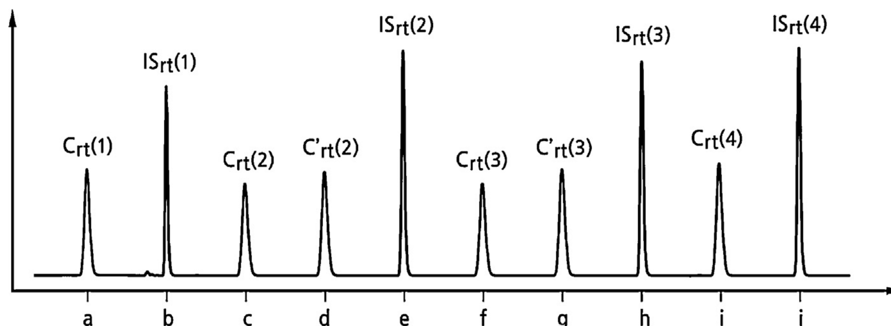

Fig. 2. An example chromatogram as a result of drug analysis.

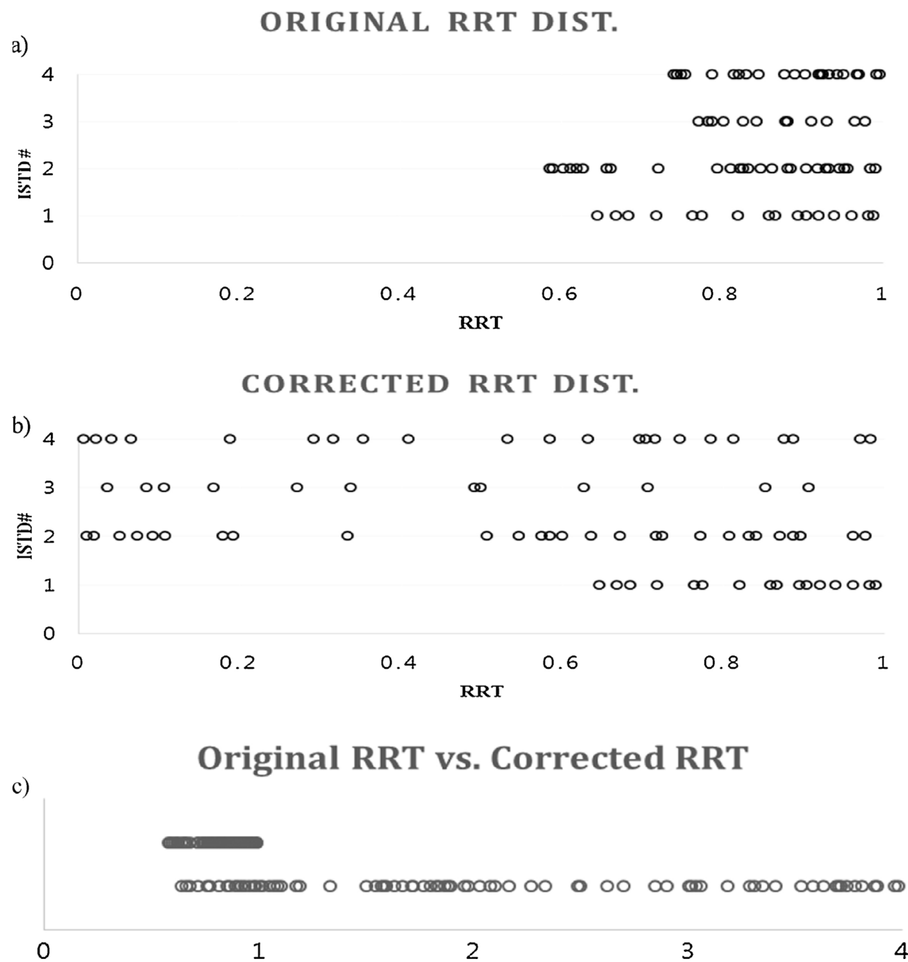

Fig. 3. The converted chromatogram of 1 MA sample (sample no. 728) and 4 ISs.

values of RRT ranged from 0 to 1, and tended to converge to 1 as the number of impurities increased. In that sense, it was more difficult to distinguish impurities on the chromatogram and the risk of overlap between RRTs increases, causing inaccuracy, resolution, and efficiency of analysis. In our previously published paper [9], we reported that the chromatograms from different origins presented at the same position, and a more complex process will be required to separate those peaks. We later introduced a new data processing module defined as Microsoft Visual Basic Application (VBA). Seven MA samples with 4 ISs were analyzed by VBA. The results were collected through the Excel file and shifts of retention time and response deviation from the sample preparation and GC-FID

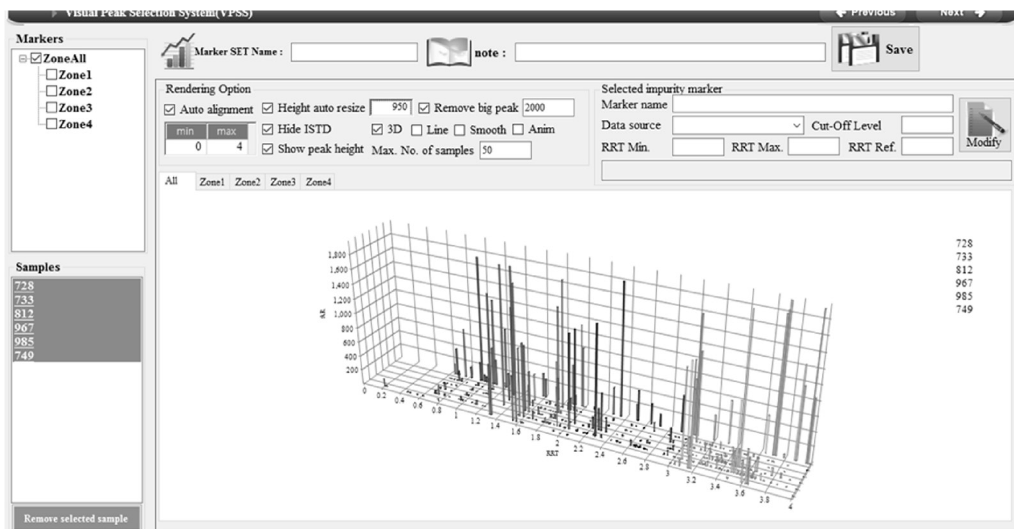

Fig. 4. High resolution of impurity profiling from 6 MA samples after application of a normalization algorithm (3D mode).

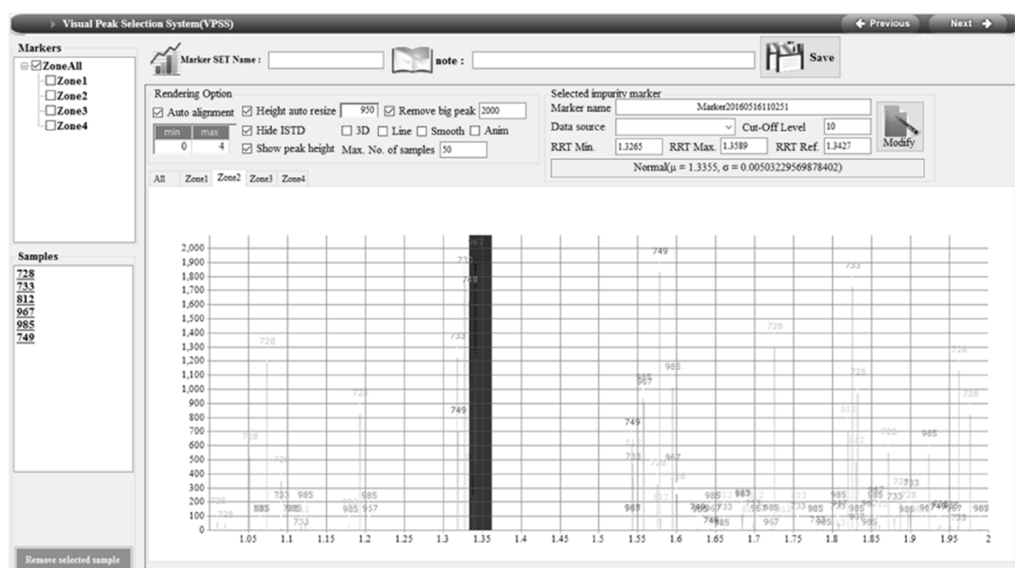

Fig. 5. The impurity peak selection on Crrt dimension by drag-and-drop of the mouse.

analysis steps were corrected [7]. According to that paper, the data processing method may not be sufficient for samples containing large numbers of impurities and ISs, nevertheless, it could reduce some errors that occur during the manual process and was time-efficient as well [7]. The conversion module used in the current study can be used for efficient classification of substance peaks even in samples containing large numbers of impurities and ISs. The full range of chromatogram can be widened so that the peaks of impurities were better aligned for easy separation and classification. It remarkably improved the resolution and kept the sequence of chromatographic peaks the same as the original.

4.2. Optimization of sample preparation and GC method

In our previously published paper [3], we reported that impurities of MA extracted by solid phase micro extraction (SPME) and LLE method showed different impurity profiles depending on volatility. Non-volatile impurities were not extracted by SPME method, but some volatile impurities and many unknown compounds were extracted only by the SPME method. Andersson et al. [32], who evaluated and compared SPE and LLE methods for impurity profiling of amphetamine, concluded that LLE was better for the amphetamine profiling method due to the uncertainty of long-term stability of SPE columns. In terms of optimizing the sample preparation method, use of the conversion module can enable comparison of the results from different extraction methods. Because it widens the full range of chromatogram and the gap between the peaks of impurities, the variation between each impurity profile from different extraction methods can be clearly compared and considered by researchers for selection of the optimized sample preparation method.

4.3. Reproducibility issue

In harmonized research of three laboratories on heroin impurity profiling, the quotient method was used for data processing and the comparison between inter-lab and intra-lab results showed some serious loss of reproducibility, despite a long collaboration between the three laboratories. The reproducibility was improved by standardizing the analytical systems of the three labs in terms of both hardware and software. In addition, they reported that the analysis in a single central laboratory is the best method so far for international comparison [17]. The quotient method used in the paper [17] could not sufficiently compensate for the variation due to systemic differences between laboratories. Standardizing the analytical hardware and software of all laboratories worldwide is practically difficult, therefore, a new data processing method that can compensate for the systemic variations between laboratories will be needed for international comparison of impurity profiles. Although no loss of reproducibility was observed in the current study since the one instrument was used in the analysis, later examination regarding whether or not the normalization algorithm can offset the systemic variations among laboratories will be valuable.

5. Conclusion

When using the relative retention time (RRT) as a criterion for classifying numerous chromatographic peaks regarding drug impurity profiling, classification of each chromatographic peak was problematic because the values of RRT ranged from 0 to 1, and tended to converge to 1 as the number of impurities in the sample increased, and the accuracy was low as well. The VPSS including the normalization algorithm was newly developed in order to resolve the problem. This is the report describing a newly developed normalization algorithm and system with application using a new equation. Because it can effectively separate each chromatographic peak by widening the full range of the chromatogram in consideration of the relative positions between all ISs and peaks of impurities, it could be a useful tool for analytical samples containing many impurities and ISs. The system's features which enable rendering and selection of impurities by all or zone through drag-and-drop user interface on the Crrt dimension cannot only provide ease of usage but also help in the decision-making of precise impurity selection. Remarkable improvement was observed in the resolution, accuracy, speed, and user-convenience of impurity profiling.

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