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Importance of Ultra Pure Water in Analytical Methods For Determination of Drug of Abuse by Mass Spectrometry

Kanak Lata Verma[1], Rohan Verma[2], Madhulika Sharma[1], RK Sarin[1], AK Jaiswal[3*]
[1]Forensic Science Laboratory, Government of National Capital Territory of Delhi, India
[2]LabWater Division, Merck Millipore, Bangalore, India
[3]Department of Forensic Medicine and Toxicology, All India Institute of Medical Sciences, New Delhi- 110029, India

*Corresponding author Dr. A. K. Jaiswal,
E-mail: ashokjaiswal72@gmail.com

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Abstract

In the recent times, a lot of molecules have seemed in the world of drugs of abuse. This always seems like an issue when it comes to the sensitive methods for identifying the sub picogram concentrations by liquid chromatography and mass spectrometry. In This Review, we will be covering the importance of the ultra pure water as one of the most important factors in the several analytical methodologies including Mass Spectrometry. In the current scenario of forensic sciences, we have the limitation to make up for the quick methods and return the reports in time. The reasons

can be various from the enough training officials to rugged developed method before samples comes to the lab for testing and how the ultra pure water makes it reproducible and reliable. Weh have seen enough of the technologies came up in last decade in terms of mass spectrometry and liquid chromatography where one can analyse 400 compounds in a run which spans around 10-20minute. But are we sure that our forensic labs are well equipped and well trained to do so. It is equally important to have the right kind of reagent used in sample preparation, mobile phases and solution preparation for standards has to be prepared with the right kind of methodologies. In the current paper a critical overview on the importance of ultrapure water at each step in a analytical method starts from the dissolving the standards, dilutions, tuning of the molecules for mass spectrometer, and so on and also the limitations of not having so in the diverse analytical approaches is provided, with a particular attention to liquid phase separation techniques coupled to high accuracy, high resolution mass spectrometer.

Introduction

Forensic science may be generally defined as a scientific search for a causal relationship between exposure to a given compound and observed biological effect. Analytical toxicology provides all the technically refined tools indispensable for detection of toxic compounds or — in other words — for the assessment of the exposure. There are version of analytical techniques which came up recently and sensitive enough and has been used for the detection of drug of abuse in cases such as drug addiction, driving under influence of drugs, neonatal drug exposure in case of drug abuse by pregnant women etc. Matrices sample remain the most widely used conventional biosample for the detection of drug of abuse. Though we don't have enough or adequate storage in our forensic facilities, we still take the sample in the absence of adequacy of results which will decide the fate of some one. There are some biological matrices such as saliva, hair, nails, tears and meconium have also been used for the same purpose. Numerous analytical techniques such as liquid chromatography with mass spectrometry (LC-MS) and LC with tandem MS (LC-MS^2), electrospray ionization Time-of-Flight mass spectrometry (ESI-TOF), combination of ultra-performance liquid chromatography (UPLC) and TOF have been used for the detection of drugs of abuse in above mentioned bio samples. These detection limits are brought ever lower, results obtained at the trace level using hyphenated techniques rely on quality and purity of the reagents used to prepare mobile phases and buffers. Because of its wide utilization and because of the volumes used in sample preparation and liquid chromatography, ultra-pure water is particularly important and extreme care must be taken with its quality. Every analytical techniques and number of biological matrices has been used for the detection of drug of abuse and has inclusion of ultra-pure water somewhere or the other. From quite long time, international forensic toxicology groups have evaluated several alternative biological matrices as diagnostic tools for drug-testing. In recent decades, growing interest has been noted in determination of drugs in alternative biological materials, mainly promoted by intensive development of highly sensitive and selective techniques, especially liquid chromatography with mass spectrometry (LC-MS) and LC with tandem MS (LC-MS2). These tools, as well as the whole analytical strategy, may be different in various toxicological disciplines. Though every technology is there, whether our forensic experts are trained enough to make use of it at most. In forensic toxicology, only those methods may be

successfully applied which combine efficient separation of the relevant compound from the biological matrix with the most specific detection. At large, LC/MS fulfils the requirements of forensic toxicological analysis due to high selectivity, possibility of detection of active metabolites, and efficient screening in unclear death cases. For this reason, also, due to gradual introduction of low-cost LC/MS instruments, this technique is now finding an increasingly important place in forensic toxicological laboratories. LC/MS underwent major evolution from last decade. From an expensive, difficult, and not always reliable hyphenated technique, it changed to a robust analytical tool, applicable in almost all analytical situations. This was caused by the introduction of atmospheric pressure ionization (API) sources. Ultra-pure water specifically needs attention as much as any analytical methodology do not only this is the part of it but also it gives the ruggedness and consistency to the analytical method.

We have seen many publications on the general aspects of LC/MS that are of relevance for forensic toxicological analysis. These studies concerned the quality of the sample and its influence on the chromatographic signal, optimization of chromatographic analysis, application of various ionization sources, and various mass analyzers in toxicology.

Separation Issues

Sample Pre-treatment Methods and Matrix Suppression

It is commonly known phenomenon that sample preparation procedure may destroy any analytical method with most sophisticated techniques. Ultra pure water becomes inseparable part of the sample preparation. This is also valid for LC/MS as well as for liquid chromatography with other detectors. It should be noted that in the conventional application some scientist tried to apply LC/MS/MS in a flow injection mode, i.e., the extracts of serum or urine were directly injected into API/MS without chromatographic separation. This procedure was checked only for a limited number of drugs (morphine, codeine, amphetamine, and benzoylecgonine) and potentially interfering compounds. Additionally, the matrix effects were not recognized [1]. Müller et al.[2] studied the effect of coextracted serum matrix on the signal of test substances — codeine (as a positive ion) and glafenine (as a negative ion). Severe ion suppression was observed for both ionization methods after the injection of serum matrix originating from protein precipitation and SPE. This says it’s no less than an offence

not accessing the matrix effect as it is the important part of the method validation. Less suppression was observed in the case of solvent extraction, while the combination of protein precipitation with SPE caused no suppression. Another fact is the diluting the sample serves an important role in subsidising the matrix effect a great deal.

For instance, In the event, you experience the matrix effect after reconstituting the final sample with 0.1ml of mobile phase, we can further dilute it to the 0.2 or 0.5ml and promising results been seen provided you have enough area under curve to get it diluted.

Another major contaminant in ultra pure water is TOC (Total organic carbon) in mobile phases, solution preparation which may pose serious challenges if not taken care (Refer Figure 1). Also organic contaminants can increase the viscosity and gelling along the matrix and overall increase the matrix effect. So it becomes important to get rid of such contaminants which will be through right selection of purification technology to make sure it doesn't add to matrix effect. It can be controlled by using water purification system with TOC monitoring so that we analyst will be aware of the TOC levels at all times.

There are diverse methods been stated that the suppression effects were caused by polar, non retained matrix components appearing on the beginning of the chromatogram. Zhou et al. [3] carried out a systematic study on the relation of matrix suppression to the extraction methods, chromatographic conditions, and concentration of analytes. In this study, blank serum matrix samples were injected into the HPLC column with the post column infusion of four test compounds at three concentration levels. The areas of suppression were located along the whole chromatogram. On the solvent front, salt and other polar unretained species were present. Other endogenous compounds were eluted later, sometimes in very high concentrations, causing severe ion suppression which was independent of the analyte concentration. There are two points here as if we have compound diluted in high TOC water used in for diluents will play major role here. Second point here is if we have the suppression irrespective of the analyte concentration as mentioned above which indicates it is the issue with the sample preparation method or chromatography and needs clean up. The basic requirement of the procedure is to have right quality of water which should be of lowest

possible TOC. Ultra pure water has to be the part of several steps mentioned above and it has to have controlled TOC and low resistivity.

Avery compared the ion suppression effects caused by extracts of human and animal (rat, dog, monkey, rabbit, and guinea pig) plasma [4]. The responses for analyte and internal standard were measured in isocratic and gradient elution, using APCI and ionspray ionization sources. It was stated that each species showed different suppression. Therefore, the validation should be performed with samples originating from the same species. Here issues is with matrix mismatch and we can imagine that if the consistency of analytical water will vary at different level of method development & validation, It will be very difficult to figure out if the issues is with the methodology or the basic water quality.

Tang et al. [5] studied matrix effects in post column-infusion experiments. Extracted blanks were injected while the ion transitions of the infused analytes were monitored. Both suppression and enhancement of ionization was observed. These phenomena were compensated by changing the ionization energy, ionization source (APCI instead of ESI), sample pre treatment method, or by including matrix ions in acquisition methods. This is the issue of incompatibility of the molecule in different ion sources and Ultra pure water can pose number of challenges if the contaminations start acting as competitor for the ionisation within the ion source.

Bansal and Liang [6] introduced two novel terms to assess the matrix effect in an LC/MS/MS assay. Matrix factor (MF) is calculated from the ratio of peak area of pure analyte to the peak area of the analyte injected together with blank matrix. Extraction uniformity (EU) is the ratio of the extraction efficiency of analyte to that of internal standard. If the EU was close to 1, it was possible to perform the validation for the same matrix from different species. This ratio of close to 1 will be achieved in the event of the extracted sample will match to aqueous standard of analyte and internal standard which suggest how good the extraction procedure should be which matches to aqueous.

LC/MS is not the panacea that will replace the optimal sample pretreatment and separation.

Ultra pure water is inseparable part of any kind of sample preparation viz Solid phase extraction(SPE), Protein Precipitation(PPT), Liquid Liquid extraction(LLE) or dilute and shoot, it become very important to have the right quality of water for all the above discussed sample preparation. Milli Q water from Merck Millipore promises the consistency and kind of purity which is acceptable by all the regulatory bodies like USP, BP and ASTM.

Composition of the Mobile Phase and Performance of Column

The composition of the mobile phase may greatly affect the sensitivity of LC/MS analysis and very tricky to trouble shoot such issues (Refer figure 2).

As discussed earlier some of the similar cases, Temesi and Law [7] studied the influence of mobile phase on electrospray response in ESI/MS, using 35 various acidic, neutral, and basic drugs as test substances. Methanol and ACN were used as organic modifiers, and ammonium acetate, ammonium formate, and TFA were used as electrolytes which have to be dissolved in high quality and contaminants free ultra pure water. Generally, in the positive ionization mode, methanol gave stronger signals than ACN. There is a known phenomenon of Electrospray response decreased with increasing concentration of ammonium acetate/formate as it increased the salt concentration and reduced the ionisation capability of compounds.

Similar issues can be visualised if we have the high TOC as contaminant in ultra pure water used for mobile phase. This happens as the high TOC increased the noise and reduce the sensitivity of the method and in turn lowest limit of quantification suffers and entire calibration curve will be off the axis. This is not possible to have the repeatability with such inconsistent base lines. Very large quantitative individual differences between drugs were observed. The authors concluded that a thorough optimization of all eluent parameters is essential for single analyte analysis which also knows as scouting for all the parameters with middle concentration of analyte (MQC). So it becomes our responsibility to not allow such issue to crop up by choosing the highest grade of ultra pure water commercially known as Milli Q Water.

According to Naidong et al.[8] reversed-phase chromatography, although widely used, is less

compatible with MS/MS detection than normal-phase chromatography. This is particularly true for highly polar compounds, which are hardly retained on reversed-phase columns, even on the mobile phase containing mostly water. A low percentage of organic phase modifier affects the sensitivity due to non optimal spraying conditions. Conversely, normal phase columns are used with a mobile phase containing high percentage of organic solvent, assuring better dispersing and evaporation of electrospray droplets. That was demonstrated in series of comparative experiments with nicotine, cotinine, and albuterol, analyzed with LC/ESI/MS/MS after separation on C18 and silica columns. The mobile phase for a reversed-phase column contained 10% acetonitrile, and for a normal-phase column, 70% acetonitrile. The sensitivity observed after normal-phase separation was distinctly higher due to the longer retention times of polar analytes and the separation from matrix compounds causing ion suppression. A similar approach was used by the same group of authors for the analysis of morphine and its glucuronides in serum [9,10] for fentanyl [11], and for hydrocodone/hydromorphone [12].

This phenomena are compound dependent and will vary from case to case but important thing which remains common in both the phase of chromatography is the contribution of water in the form of mobile phase acting as one of the deciding factor of separation which gives the strength to mobile phase to interact with compounds more closely in comparison to the organic modifier. Different Compounds behaves differently in different concentration of TOC present in water as buffer and their direct impact will be very obvious on the sensitivity of the method.

Detection Issues

Choice of Ionization Source

As we have studied in past, there are most used techniques which is generally been adopted for the 80-90 percent of methods are API due to overwhelming compatibility of this source in the LC/MS of large molecules. However, the choice of ESI or APCI will vary for particular substances. As a rule, the response of ESI for very polar substances is higher than that of APCI. On the other hand, less polar compounds, including a majority of parent drugs, need an active ionization mode for better Detectability. It is therefore a good practice to try both

ionization sources in the developing stage of the method. Unfortunately, this approach is not often followed or not reported in the literature. Nevertheless, some studies were specifically devoted to the usefulness of various ion sources in toxicological analysis. As we have mentioned earlier as ultra-pure water is the prominent part of ionisation and charge transfer and it has to be free of ions as this contribute in transferring the charges to the molecules and give rise to the formation of adducts which may lead quantifying the wrong precursor. Sometime these precursor gives good sensitivity but a non rugged method and gives a lot of troubles while validation as these adduct are inconsistent and coming from the contaminants which itself is inconsistent in the purified water used for mobile phase preparation.

Dams et al. carried out a comparative performance study of the three ion sources for the ion-trap–based mass spectrometer (pneumatically assisted ESI, sonic spray, and APCI), using morphine as a model compound analyzed under different elution conditions. The influence of solvent modifier, buffer, pH, and volatile acids was studied. The composition of the mobile phase had a serious impact on the ionization efficiency. Strong similarities were observed between the performance characteristics of ESI and sonic spray, whereas APCI showed completely different behavior. The authors concluded that APCI source showed the greatest potential, due to robustness, applicability to higher flow rates, and positive response to acids or buffers [13].

Here is a study done by Stéphane Mabic [14] where the effect of the presence or the absence of UV lamp in water purification systems. The function of UV lamp is to reduce the organic contaminant. The chromatogram baseline was higher with no UV lamp. This directly impacts the LLOQ (Lower limit of Quantification) in analytical method. This also increase the danger of fluctuating the correlation coefficient of calibration curve which itself is a failure and will pose repeatability issues for the unknown sample. This highlights the fact that it is very important to monitor on-line TOC level in water in order to always be aware of the quality of the water quality.

If we talk about any ionisation mode other than MALDI, we have a lot of scope of contamination from water used in reagent and solution preparation and drop the sensitivity

within the ion source. In some cases, Mobile phase are introduced along with the tuning mixture containing compound it is aqueous part is involved in ionisation and competing against the analyte of interest to reduce the area under curve in final stages of chromatography.

Choice of Mass Analyzer (Q vs. QQQ vs. IT vs. qTOF)

It goes without saying that the use of tandem mass spectrometry instead of single stage quadrupole gives obvious advantages concerning specificity and sensitivity. The main obstacle of LC/MS/MS is the cost. However, in the last few years some manufacturers launched lower-cost bench-top tandem instruments that may be widely applicable in forensic toxicological laboratories.

Some research groups performed comparative studies concerning various mass analyzers applied in LC/MS.

These mechanism of ion travelling happened inside the vacuum so water doesn't really create issues directly but as discussed earlier If source of ultra pure water is not appropriate in earlier stages of ion generation where mobile phase preparation, sample preparation, sample treatment plays defined role in the diverse ion sources, results can be wayward and quantification can be hampered due to in consistency. In the following examples, we have discussed some Analysis of forensic molecules with the various mass analysers with the explained credibility.

Clauwaert et al.[15] applied the LC/ESI/qTOF/MS for quantitative measurements of MDMA and its metabolite MDA in body fluids. The LOQ was 1mg/l and the linear dynamic range extended over four decades. It was concluded that this technique achieves the linear dynamic range for LC/ESI/MS/MS.

Zhang and Henion[16] compared the applicability of LC/ESI/qTOF/MS and LC/ESI/MS/MS for quantitative analysis of idoxifene in human plasma. The drug and its deuterated analog as an internal standard was isolated from plasma using a semi automated 96- well hexane

extraction and separated on a 30 mm ¥ 2 mm CN column. This column could separate target compound from the matrix, which was not possible with the ODS column. For the TOF/MS instrument, an exact mass of the protonated quasi-molecular ion was measured (m/z 524.1441), whereas a MS/MS instrument was applied in SRM mode, using m/z 524.2 as a parent ion and m/z 97.9 as a product ion. The comparison showed that the LC/MS/MS technique was about ten times more sensitive than LC/qTOF/MS (the LOQs for idoxifene were 0.5mg/l and 5mg/l, respectively). Both methods showed satisfactory dynamic range. In conclusion, the authors stated that LC/qTOF/MS might be used to complement LC/MS/MS in certain cases.

Comparison between an ion trap and single-stage quadrupole mass spectrometer was done for GC/MS by Vorce et al.[17] The authors compared the sensitivity, precision, and stability of ion ratios obtained for both mass analyzers,using urine extracts spiked with amphetamine, methamphetamine,

THC-carboxylic acid, phencyclidine, morphine, codeine, 6-monoacetylmorphine, and benzoylecgonine on five concentration levels for each drug. The sensitivity of the ion trap used in the full-scale mode was comparable to quadrupole, working in the selected ion monitoring mode. The advantage of the ion trap was that it provided a full spectrum of substances. The ion ratios were slightly more precise for quadrupole. These data may be also useful for the assessment of ion trap LC/MS.

Open problems and Future Trends

Existing needs and observed trends of development allow predicting the main pathways of progress in LC/MS applied for forensic toxicology.

LC/MS will cover practically the whole spectrum of compounds of toxicological relevance. The use of LC/MS as a tool for general screening procedures will be common, and the libraries of mass spectra will be available with any purchased instrument. Most probable will be combined use of in-source CID for preliminary screening with consecutive MS/MS confirmation. The use of Ultra pure water makes it even more indispensable as it minimizes

any failure of experiments from the hardware or the sample treatment.

As we have discussed earlier, the issues of matrix effects due to multiple reason and how the bad quality of ultrapure water can make it even worsen the situation so it's important to take the control on factors which are under our capabilities as quality of ultra pure water is one of those. Milli Q water gives us the liberty to do so and from there on we can work on the other important steps like sample preparation, chromatography & ion source selection to get rid of the matrix effect. It has been mentioned in one of the recent review and saying goes like this - If the "specter" of Drugs of abuse haunts the community of drug addiction experts, another phantom is haunting forensic analysts who use liquid chromatography coupled to mass spectrometry: the so-called "matrix effect"[18] . It is widely agreed that the term "matrix effect" defines the "direct or indirect alteration or interference in response due to the presence of unintended analytes and or organic impurities from the water or other interfering substances in the sample or poor sample preparations'[19].

From a careful reading of the existing literature, a few considerations can be drawn which impact directly the analysis of the drugs of abuses, which are summarized below.

- At every step of analytical chemistry and in this vary case the forensic sample analysis, there is a huge impression of the ultra pure water (Milli Q Water) in method development and validation viz sample preparation, liquid chromatography, Ion transfer in mass spectrometer

.

- In electrospray, LC–MS, a matrix effect can always occur when dealing with complex and non-standardized samples. As mentioned several times in this review that there are various way to reduce the matrix effect and Ultra pure water makes an important one which checks the interference from TOC and ionic contamination which in turn may pose a lot of challenges.

- The matrix effect affects not only the analytical sensitivity but also the inter-sample reproducibility of the instrumental response; although with some limitations (e.g.,

mutual ion suppression or enhancement), the use of stable-isotope-labelled internal standards is generally regarded as the method of choice to reduce to a minimum the risk of analytical inaccuracy caused by the matrix effect, but this applies only to the unlabeled analog, not to other structurally related compounds.

- The presence of organics has a more significant impact on MS detection. It is important to use high purity water with a very low TOC level to prepare samples and run the LC. This is achieved when using freshly produced water in the laboratory. Because of the way they are utilized, double distilled water and HPLC grade bottle water easily gain organics. This implies higher TOC levels and in result, poorer baselines.

- Online Monitoring of these contamination level (TOC & Resistivity) gives us an upper hand to have the control on such contamination and keep them at check. These monitoring devices with the validation give a laboratory a hold on the regulatory requirements as well.

- Validation and qualification of the water purification system also allow certifying the good quality of ultrapure water used in certified laboratories.

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Special vote of thanks to the book from Jehuda Yinon on Advances in Forensic Applications of Mass Spectrometry which reflects a lot of ideas on the advancement in Forensics. Having all the information required for the novice to start the study on forensics (See Reference 20).

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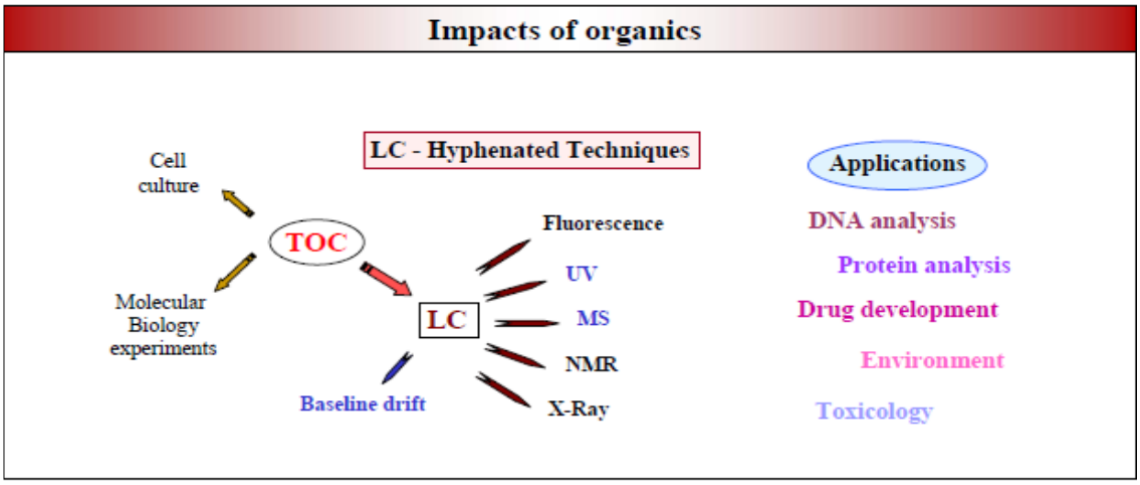

Figure 1. Low TOC ultrapure water: Reagent for LC-MS Reference: Stéphane Mabic and Cecilia Regnault, Research and Development - Lab Water Division – Millipore

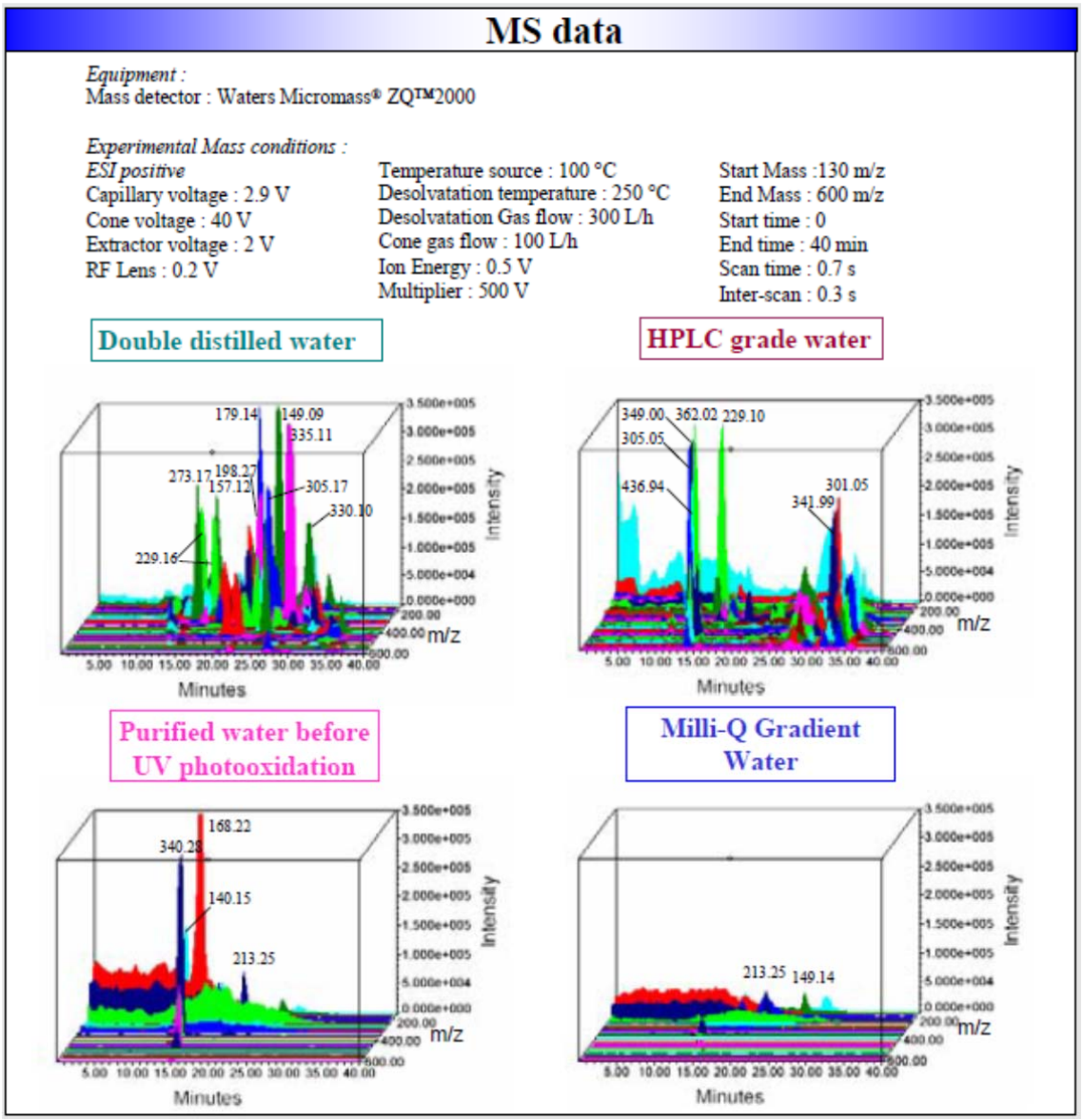

Figure 2. The impact of low level organics on HPLC and LC/MS baselines of ultrapure water

Reference: Cecilia Regnault, Research and Development - Lab Water Division – Millipore

Authors Column

Dr. Ashok Kumar Jaiswal has completed his post graduation and Ph.D. degree in chemistry from Gorakhpur university, Gorakhpur. Presently he is working as Chemist in the Department of Forensic Medicine and Toxicology, All India Institute of Medical Sciences, New Delhi. He has 20 years of research and analysis experience in field of Analytical Chemistry. He has guided several MD and Ph.D. students in the institute, published 100 research papers and 03 books.

Dr. Jaiswal is members of several scientific bodies/societies of national and international repute. He is on board of referees of the Indian Police Journal, Associate Editor of International Journal of Medical Toxicology and Legal Medicine and Member of Scientific Council of Journal of Forensic Medicine and Toxicology.

Dr. Jaiswal has received Prof. K.A. Thaker award in 2009 and Dr. P.D. Sethi annual certificate of merit award in 2008.

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