DOCUCHEM WHITE PAPER SERIES

Impact of Solvent Quality in the outcome of the API purification processes

Dr. Jordi Bacardit

Ph.D in Organic Chemistry, Peptide Chemist by vocation, formulator and analyst by training and experience. Leading the Uatane Pharma network and the Docuchem team that help Pharma and API industries resolve issues with their processes and analytical methods.

jbacardit@docuchem.com
jbacardit@uatane.com
Mob. +34648056707

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1 Introduction

The presence of impurities in solvents used during the purification of drug substances can have significant impacts on the quality, safety, and efficacy of the final pharmaceutical product. The consequences of using solvents of insufficient quality can have a broad impact on the following aspects:

Chromatography

Column Fouling: Polymeric impurities can cause fouling of chromatographic columns, leading to reduced column efficiency, shorter column life, and increased maintenance costs.

Baseline Noise: These impurities can increase baseline noise, making it difficult to detect and quantify the drug substance and other components accurately.

Crystallization:

Crystal Quality: Polymeric impurities can interfere with the crystallization process, leading to poor crystal quality, polymorphism issues, and lower purity of the final drug substance.

Drug Formulation:

Product Stability: Polymeric impurities can affect the stability of the final drug formulation, potentially leading to reduced shelf life and efficacy.

Safety: Some polymeric impurities may be toxic or cause adverse reactions, posing risks to patient safety.

2 Types of Impurities in Solvents

2.1 Chemical Impurities:

Organic Impurities: These can include degradation products, residual reactants and by-products from the solvent manufacturing and purification process like extractables (mostly polymers).

Inorganic Impurities: Trace metals, salts, and other inorganic compounds that may be present due to the solvent production or storage conditions.

2.2 Physical Impurities:

Particulate Matter: Dust, fibers, and other particulate contaminants that can be introduced during solvent handling and storage.

3 Impact on Drug Substance Purification

3.1 Quality of the Drug Substance:

Purity Levels: Impurities in solvents can co-elute with the drug substance during purification processes like crystallization, distillation, or chromatography, leading to lower purity levels of the final product.

Impurity Profiles: Unwanted impurities may introduce new, unidentified peaks in analytical chromatograms, complicating quality control and regulatory approval processes.

3.2 Safety and Efficacy:

Toxicity: Some impurities, even in trace amounts, can be toxic or have adverse effects, posing risks to patient safety.

Drug Efficacy: Impurities might interfere with the drug's pharmacological activity, reducing its effectiveness.

3.3 Regulatory Compliance:

Guidelines: Regulatory agencies like the FDA and EMA have strict guidelines on the acceptable levels of impurities in drug products and solvents. Non-compliance can lead to batch rejections, recalls, and regulatory actions.

Validation: Ensuring solvent purity is crucial during the validation of purification processes to demonstrate that the process consistently produces a product meeting its predetermined specifications.

4 Managing Solvent Impurities

4.1 Solvent Selection:

High Purity Solvents: Using solvents of pharmaceutical or analytical grade with low impurity levels can mitigate the risk of contamination.

Supplier Qualification: Selecting reputable suppliers who provide consistent quality and documentation for their solvents.

4.2 Purification Techniques:

Filtration: Removing particulate matter through filtration techniques before using solvents.

Distillation: Purifying solvents through distillation to remove volatile organic impurities and non-volatile residues.

Adsorption: Using activated charcoal or other adsorbents to remove specific impurities from solvents.

4.3 Analytical Monitoring:

Routine Testing: Regularly testing solvents (in concentrated form) for impurities using techniques like HPLC, GC, ICP-MS, or NMR to discriminate in between good solvent and better solvents is key to successful purification processes.

In-Process Controls: Implementing in-process checks during drug purification to monitor and control solvent quality.

5 Impurities in solvents commonly used for preparative purification

5.1 Common to all solvents

5.1.1 Polymeric impurities

Polymeric impurities in purification solvents can arise from several sources and pose significant challenges in the pharmaceutical and analytical industries. These impurities can affect the efficiency of purification processes and the quality of the final drug substance. Here's an overview of polymeric impurities in purification solvents, their sources, impacts, and management strategies:

5.1.1.1 Sources of Polymeric Impurities

Degradation Products:

Solvent Decomposition: Over time and under certain conditions (e.g., exposure to heat, light, or oxidizing agents), solvents can decompose and form polymeric materials.

Stabilizer Breakdown: Some solvents contain stabilizers to prevent degradation, but these stabilizers can themselves degrade and form polymeric impurities.

Contamination:

Manufacturing Residues: During solvent production, residues from polymeric materials used in the manufacturing process can contaminate the solvent.

Storage and Handling: Solvents stored in plastic or polymer-lined containers can leach polymeric substances, especially if the solvents are stored for long periods or under suboptimal conditions.

Reaction By-products:

Chemical Reactions: Solvents can participate in unintended chemical reactions during synthesis or purification processes, leading to the formation of polymeric by-products.

5.1.1.2 Detection and Characterization of Polymeric Impurities

Size-Exclusion Chromatography (SEC): Effective for separating and analyzing polymeric impurities based on their molecular size.

Fourier-Transform Infrared Spectroscopy (FTIR): Useful for identifying specific functional groups present in polymeric impurities.

Nuclear Magnetic Resonance (NMR) Spectroscopy: Provides detailed structural information about polymeric impurities.

Liquid Chromatography coupled to Mass Spectrometry (MS): Can be used to identify the polymeric impurity and to determine the molecular weight and the structure of polymeric impurities.

Reversed Phase HPLC with UV or RID detectors: Can be used to determine the molecular weight and structure of polymeric impurities.

5.1.1.3 Managing Polymeric Impurities

Solvent Selection:

High-Purity Solvents: Use solvents of pharmaceutical or analytical grade with stringent specifications for impurity levels.

Stabilized Solvents: Choose solvents stabilized against degradation if polymeric impurities are a known issue.

Storage and Handling:

Appropriate Containers: Store solvents in containers made of materials that do not leach polymeric substances.

Controlled Conditions: Store solvents under recommended conditions (e.g., cool, dark environments) to minimize degradation.

Purification Techniques:

Filtration: Use high-efficiency filters to remove polymeric particles from solvents before use.

Distillation: Purify solvents through distillation to remove high-molecular-weight polymeric impurities if your supplier is not providing the desired quality.

Regular Monitoring:

Quality Control Testing: Implement routine testing of solvents for polymeric impurities using appropriate analytical methods on concentraded (evaporated) samples.

In-Process Controls: Monitor solvents during purification processes to detect and address the presence of polymeric impurities promptly.

5.1.2 Inorganic Impurities

Metal Ions: Trace amounts of metals such as iron, copper, and sodium can be present due to contact with metal surfaces during production, storage, or transportation.

Chloride and Sulfate Ions: These can be introduced from various sources during manufacturing or handling.

5.2 Examples of Specific solvent related impurities.

5.2.1 Acetonitrile

Acetonitrile (CH_3CN) is a commonly used solvent in pharmaceutical and analytical applications due to its favorable properties, such as high polarity, low viscosity, and good miscibility with water and many organic solvents. However, like any chemical, it can contain various impurities that can impact its performance and suitability for specific uses. Here are the typical impurities found in acetonitrile:

Acetamide (CH_3CONH_2): Formed through the hydrolysis of acetonitrile, especially in the presence of water or acidic conditions.

Acetic Acid (CH_3COOH): Can be a degradation product of acetonitrile, often formed through oxidative processes.

Ammonia (NH_3): Can be present as a residual impurity from the manufacturing process.

Other Nitriles: Minor quantities of other nitriles like propionitrile (CH_3CH_2CN) can be present due to incomplete purification during production.

5.2.2 Methanol

Methanol (CH_3OH) is a widely used solvent in pharmaceutical and analytical applications due to its polarity, low boiling point, and miscibility with water and organic solvents. However, methanol can contain various impurities that can affect its suitability for specific uses. Here are the typical impurities found in methanol:

Formaldehyde (CH_2O): Formed by the oxidation of methanol, especially when exposed to air and light.

Acetone (CH_3COCH_3): Can be present as a manufacturing by-product or as a degradation product.

Ethanol (C_2H_5OH): Often present in trace amounts due to the fermentation processes or contamination from other alcohols.

Dimethyl Ether (CH_3OCH_3): Can be a by-product of methanol synthesis or formed through dehydration reactions.

Methyl Formate ($HCOOCH_3$): Can form through reactions between methanol and formic acid.

Benzene (C_6H_6): A potentially hazardous impurity, benzene can be present in trace amounts due to incomplete removal during production.

5.2.3 Hexane

Hexane (C_6H_{14}) is a commonly used solvent in the pharmaceutical and chemical industries, particularly for extraction processes, chromatography, and as a cleaning agent. However, hexane can contain various impurities that can affect its performance and suitability for specific applications. Here are the typical impurities found in hexane:

Other Hydrocarbons:

Isomers of Hexane: Hexane can contain various isomers, including n-hexane, 2-methylpentane, 3-methylpentane, and 2,3-dimethylbutane. The presence of these isomers is typical since commercial hexane is usually a mixture of these compounds.

Heptane (C_7H_{16}): Can be present due to incomplete separation during the refining process.

Pentane (C_5H_{12}): Another common impurity from the distillation process.

Aromatic Hydrocarbons:

Benzene (C_6H_6): A potentially hazardous impurity, benzene can be present in trace amounts due to incomplete removal during production.

Toluene (C_7H_8): Another aromatic compound that may be present as a minor impurity.

Unsaturated Hydrocarbons:

Olefinic Compounds: Hexane may contain small amounts of unsaturated hydrocarbons such as hexenes due to the manufacturing process.

5.2.4 Ethyl Acetate

Ethyl acetate ($C_4H_8O_2$) is a commonly used solvent in the pharmaceutical, chemical, and food industries due to its low toxicity, pleasant odor, and excellent solvency properties. However, like any solvent, it can contain various impurities that may affect its performance and suitability for specific applications. Here are the typical impurities found in ethyl acetate:

Organic Impurities

Ethanol (C_2H_5OH): Ethanol is a common impurity due to incomplete esterification during the production process.

Acetic Acid (CH_3COOH): Acetic acid can be present as a residual reactant or a by-product of the hydrolysis of ethyl acetate.

Acetaldehyde (CH_3CHO): Formed through the oxidation of ethanol or as a by-product during the production process.

Water (H_2O): Ethyl acetate is hygroscopic, meaning it can absorb moisture from the air, leading to water as a common impurity.

Methanol (CH_3OH): Methanol may be present as a by-product of the esterification process or as a contaminant from raw materials.

Butyl Acetate ($C_6H_{12}O_2$): Another ester that can be present due to cross-contamination during manufacturing processes.

Identifying impurities in crude drug substances is crucial for the success of purification processes in the pharmaceutical industry. The presence and nature of these impurities can significantly affect the efficiency and effectiveness of purification methods, as well as the safety, efficacy, and quality of the final pharmaceutical product. Here are the key reasons why identifying these impurities is important:

6 Case study for solvents sourced in India.

6.1 Materials and methods

Samples of Solvents for quality evaluation were procured locally in Ambernath (Maharashtra) by ChiroChem Laborotories who evaporated under reduced pressure 1 liter of solvent of each supplier until only 2 mL were remaining. The samples were sent to Docuchem SLU (Spain) for testing by GC, HPLC, LCMS as compared to non evaporated samples of HPLC quality grade solvents sourced in Spain by Docuchem.

Four different brands were selected which will be described in this paper as Brand 1, Brand 2, Brand 3 and Brand 4.

	AcN Hplc	MeoH Hplc	DCM Hplc	AcN LR	MeOH LR	DCM LR	AcN AR	MeOH AR	DCM AR	MeOH Com	DCM Com
Brand 1	X	X		X	X	X	X	X	X		
Brand 2										X	X
Brand 3	X	X	X						X		
Brand 4	X	X	X	X	X	X		X			

The evaporated samples were then tested by GC, HPLC and LCMS by the following methods:

HPLC

Flow: 0.6 mL/min
Column: Zorbax Extend-C18 50x2.10 mm in 1.80 micron
Mobile phase A: Water 0.1 % Formic acid
Mobile phase B: MeOH 0.1% Formic acid
Injection volume: 10 microliters
Gradient: 5-95% B in 15 min, 95%-5% in 1min, 5% equilibration for 9 min.
Column Temp. 35ºC
Detection: PDA from 190 to 400 nm.

LCMS

Flow: 0.6 mL/min
Column: Zorbax Extend-C18 50x2.10 mm in 1.80 micron
Mobile phase A: Water 0.1 % Formic acid
Mobile phase B: MeOH 0.1% Formic acid
Injection volume: 10 microliters
Gradient: 5-95% B in 15 min, 95%-5% in 1min, 5% equilibration for 9 min.
Column Temp. 35ºC
Detection: ESI (+) on QQQ Shimadzu LCMS 8060 with Nexera HPLC
Nebulizing gas Flow: 3 mL/min
Heating gas Flow: 10 mL/min
Interface temperature: 400ºC
Dessolvation temperature: 650ºC
DL Temperature: 250ºC
Heating block temperature:400ºC
Drying gas Flow: 10 mL/min
Q3 Scan from 50 to 1000 dalton

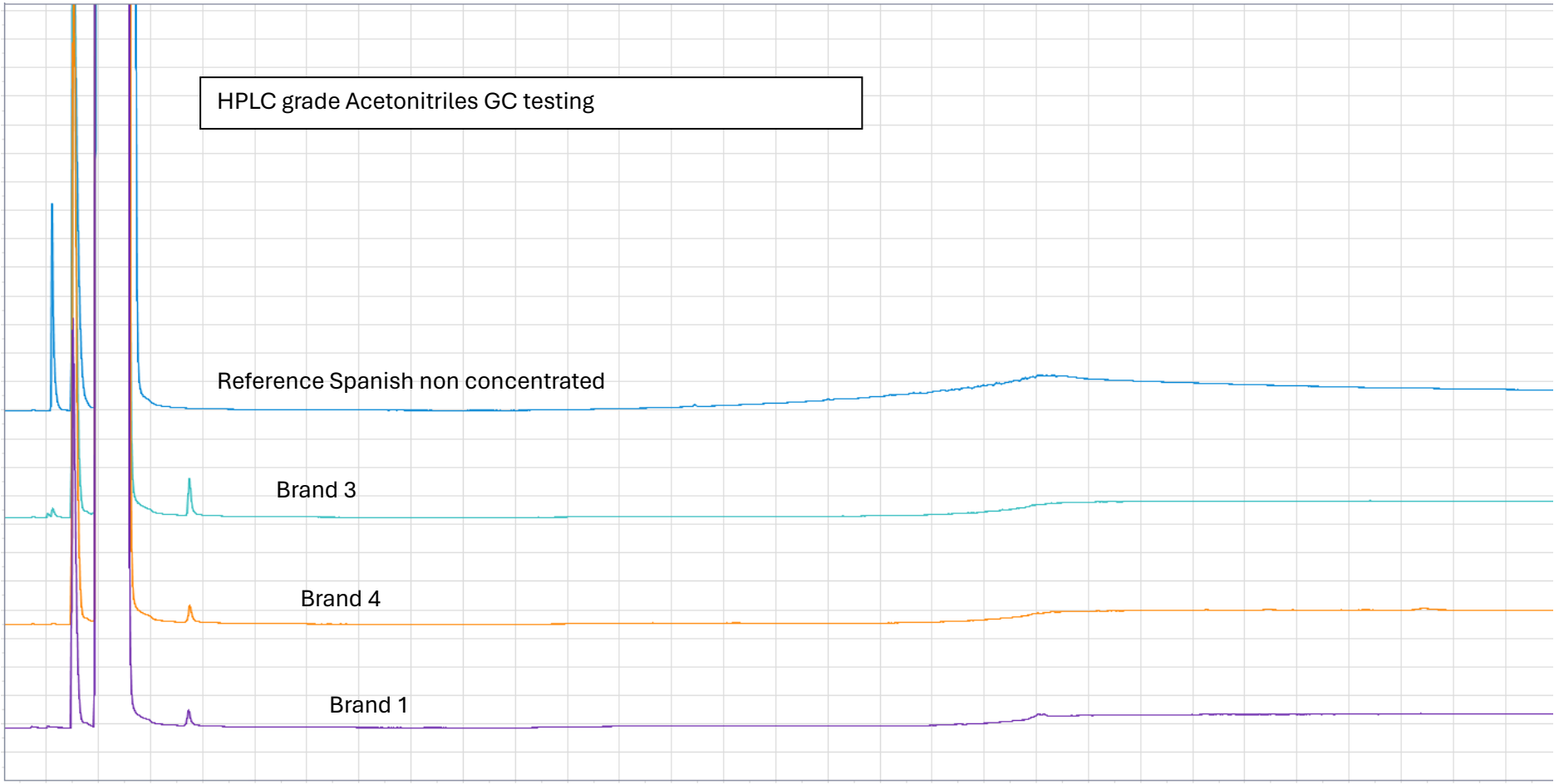
GC

Column: DB-624 30 m x 0.53 um x 3 um
Run time: 60 min
Oven Temp: 40ºC
Rate: 10ºC/min
Final Temp: 240ºC
Hold time: 20 min
Inj. Volume: 1 uL
Det. Temp: 140ºC

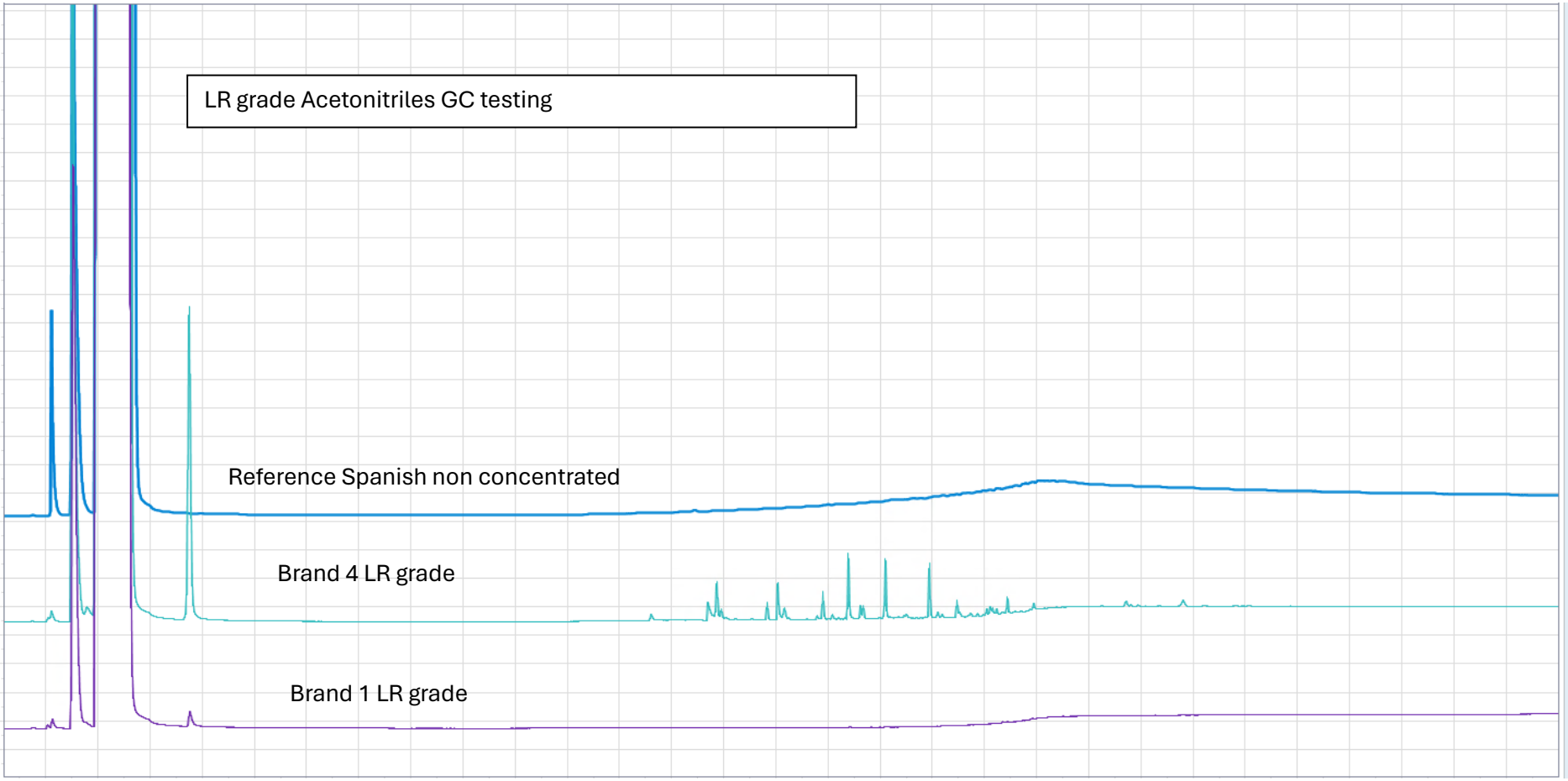
Split ratio: 1:1
Pressure: 22.6 kPa
Average velocity: 32 cm/s
Control mode: Constant Flow
Flow: 4.4 mL/min
Det. Temp: 250ºC
H2 flow: 40 mL/min
Air Flow: 400 mL/min
Make up Flow: 40 mL/min

7 Results and discussion

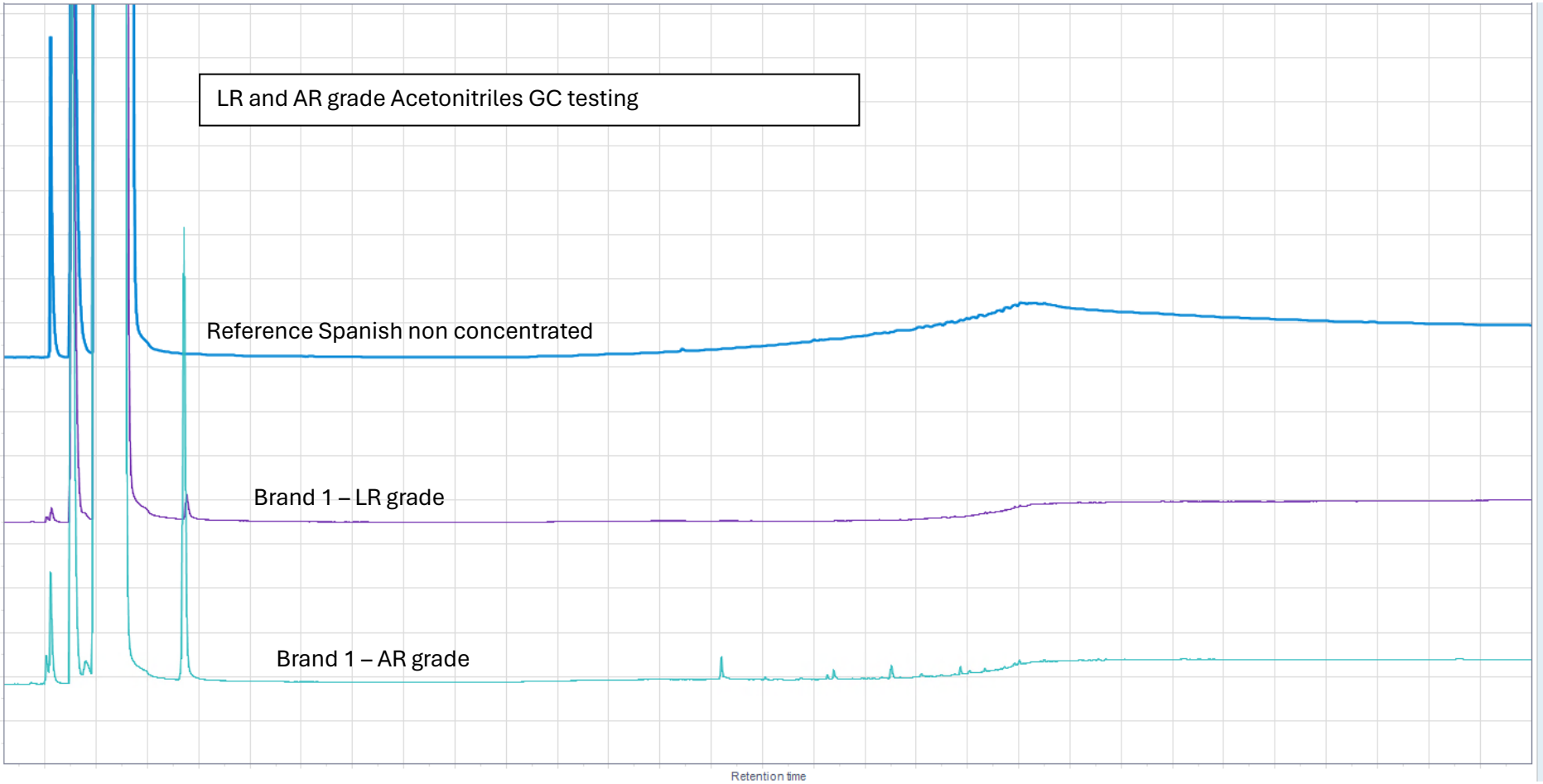
The following comparisons allow to ascertain the number of impurities present that can be detected and the differences that one can find in between different manufacturers for the same grade of product.



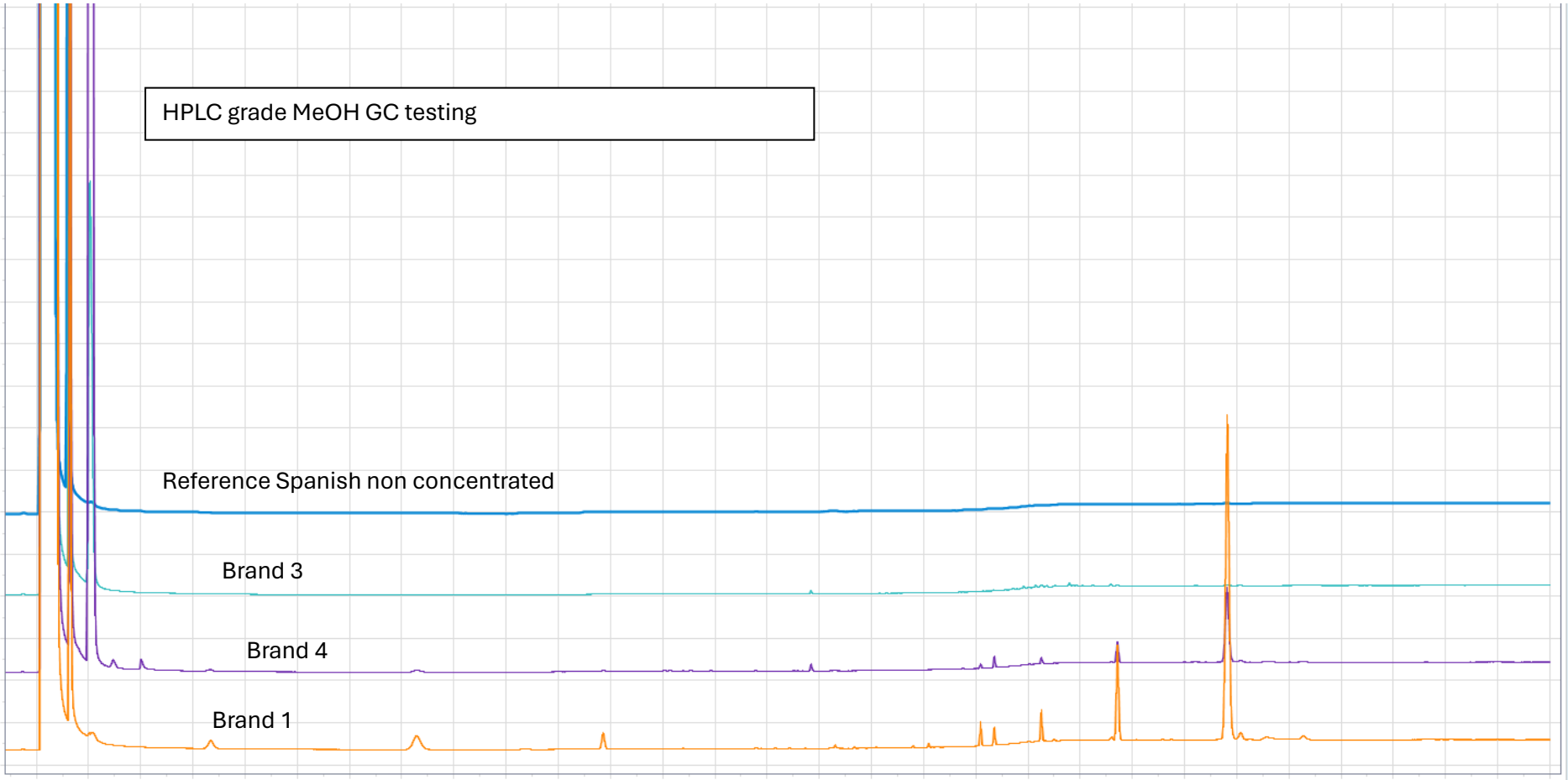
AcN HPLC from different brands. Top Spanish reference brand non concentrated then Indian brand3, Brand 4 and Brand 1. The best quality is for Brand 1 although Brand 3 and 4 are also showing quite aceptable quality.



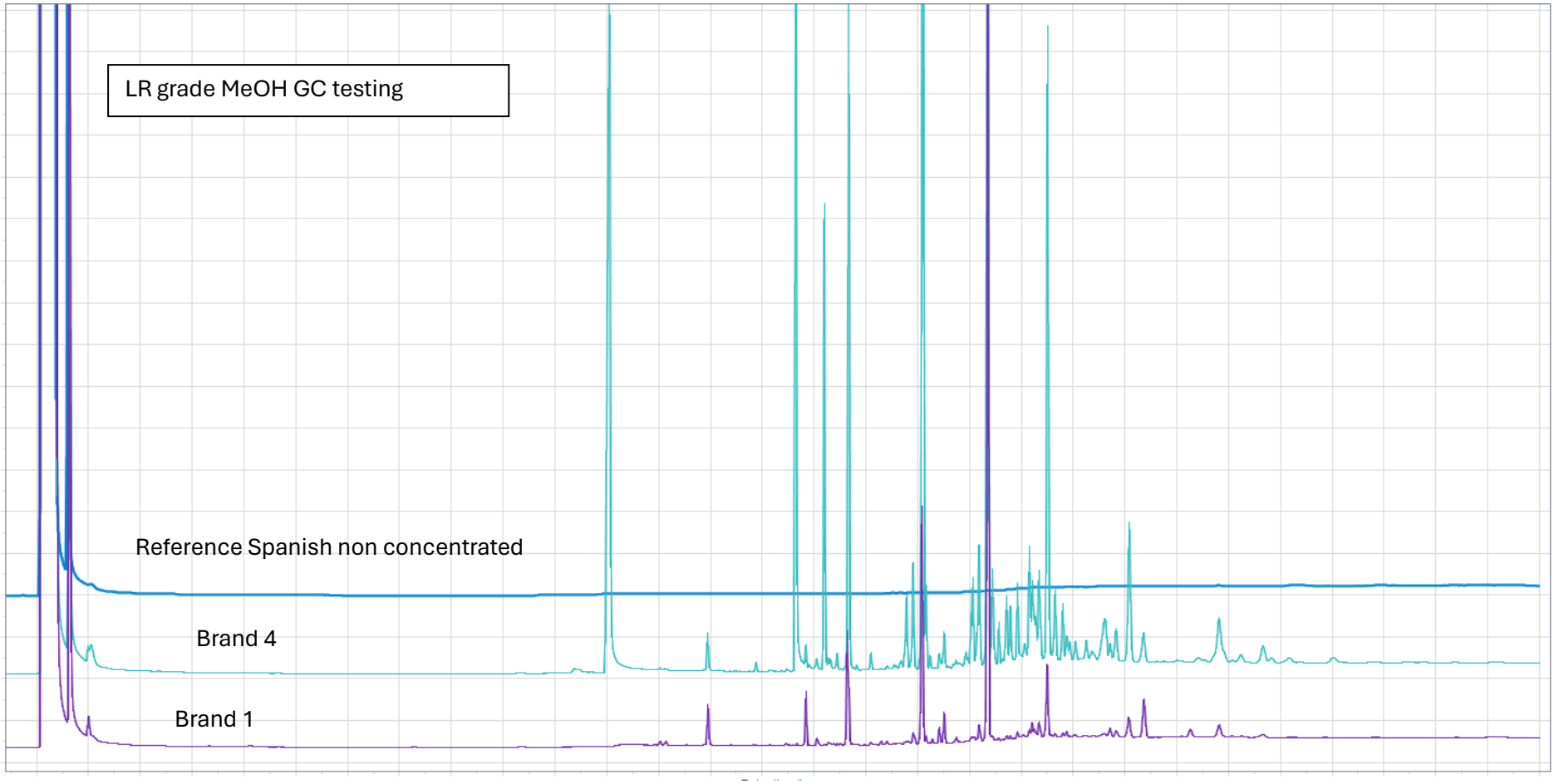
AcN HPLC grade from spanish Brand as compared to Brand 4 LR grade and Brand 1 LR grade. Brand 1 continues to have better quality in acetonitrile as compared to Brand 4 and even its LR grade quality could be considered for us in purification.



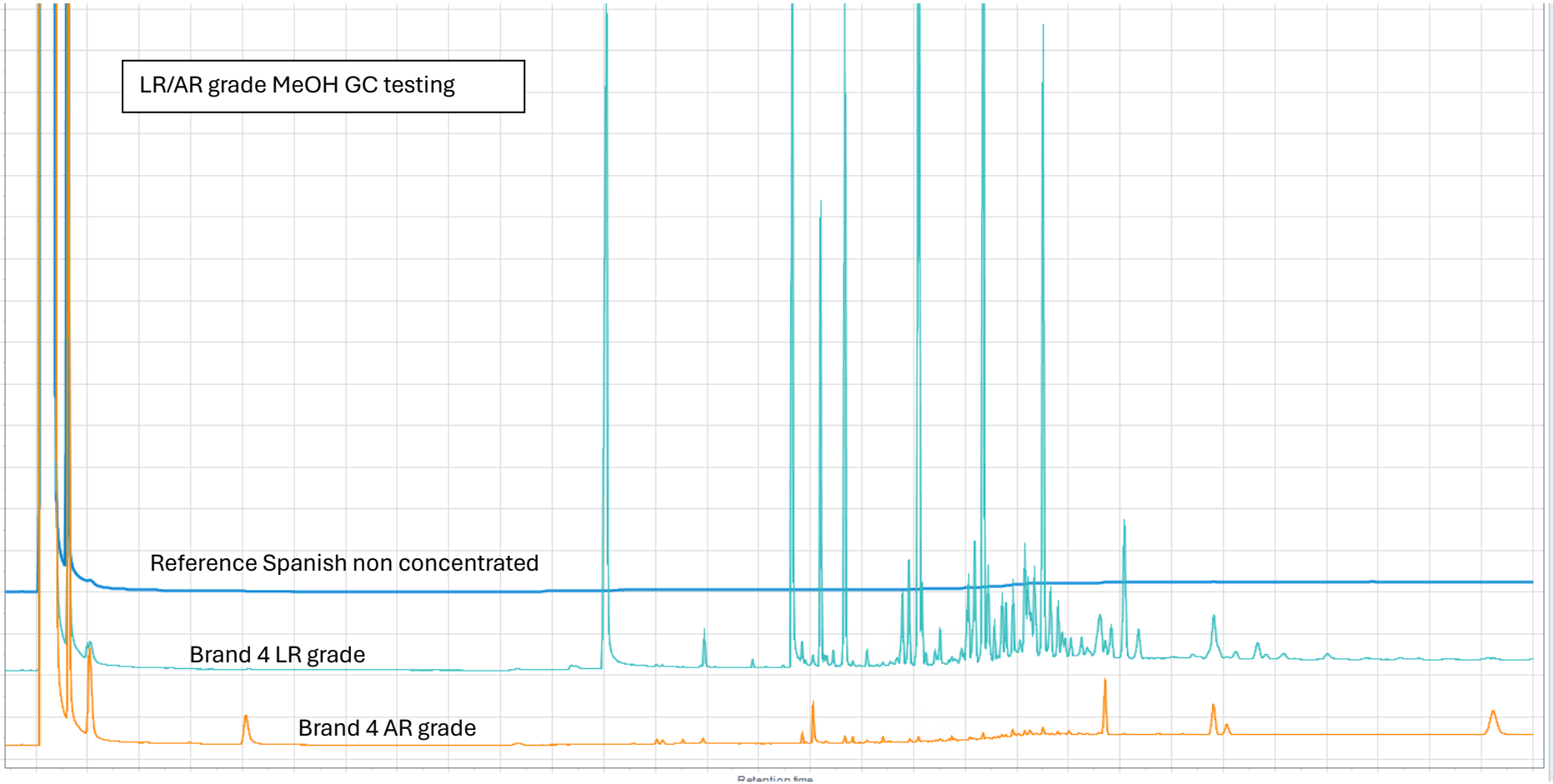
AcN HPLC grade from spanish Brand. Brand 1 LR and last is Brand 1 AR grade. As it can be seen, quality of the Brand 1 AR and LR grades are not ver different and surprinsingly the quality of LR grade here is better than AR grade. That can naturally change from batch to batch ans it is the responsibility of the user to actually set the quality specs for evaporated material on the basis of the success of its purificaiton using it.



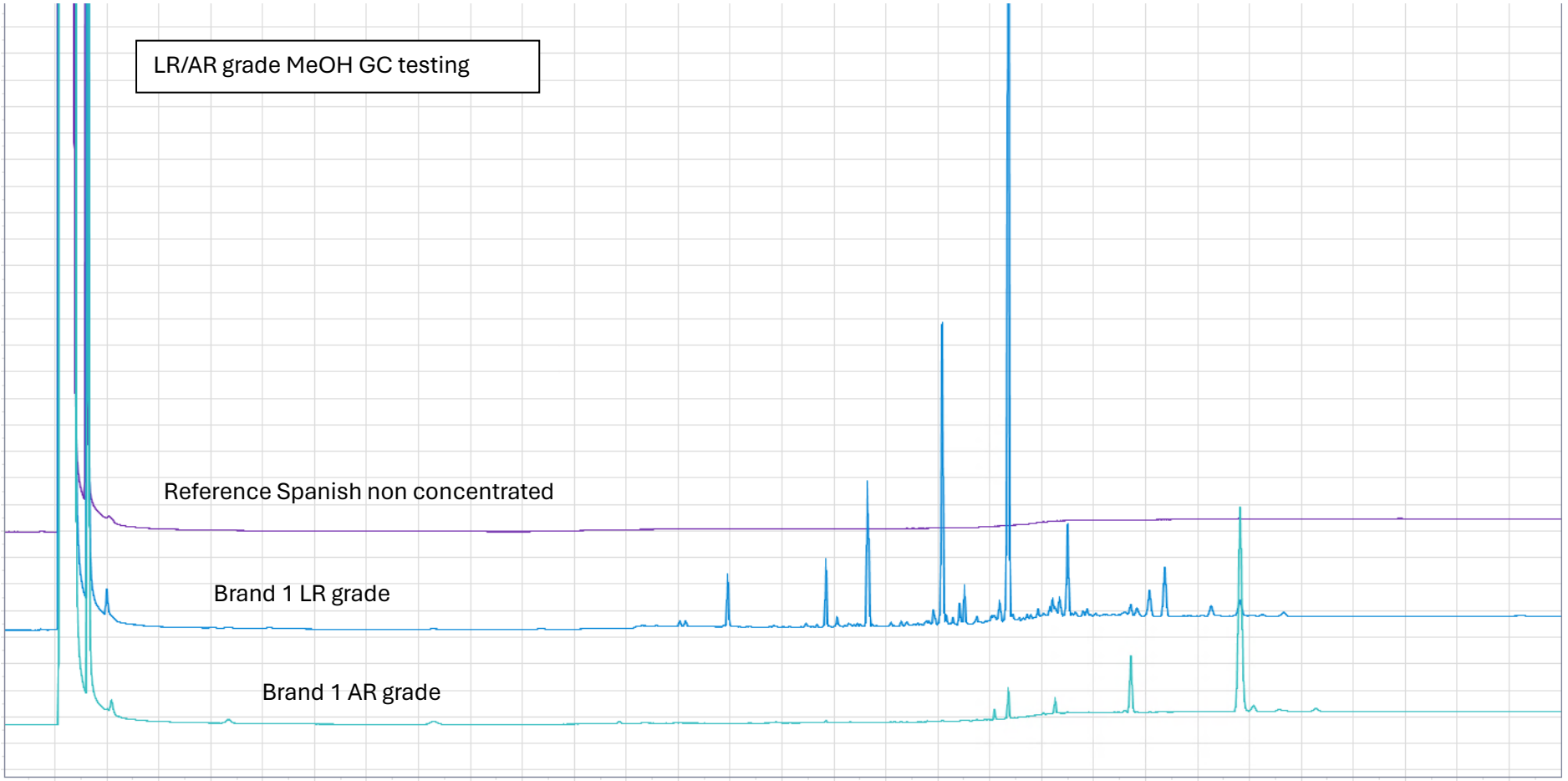
MeOH HPLC spanish Brand. MeOH indian brands HPLC grade from Brand 3, Brand 4 and Brand 1. While Brand 1 was comparatively better than brand 4 for acetonitrile, in the case of MeOH that is not the case, meaning that the supplier manufacturing process and origin of the crude that they buy is as important as the care that the manufacturer applies to the purification.



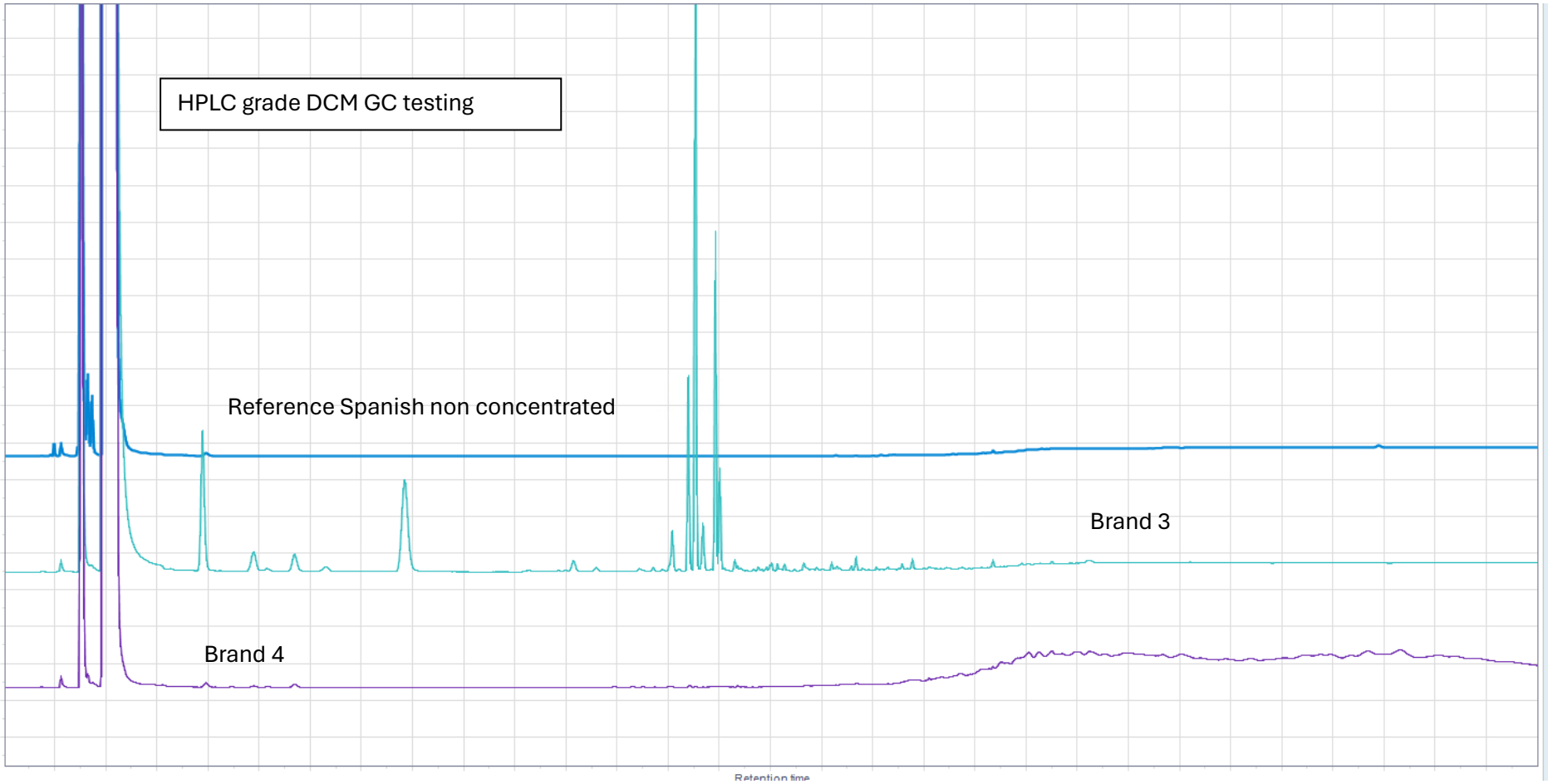
MeOH reference HPLC spanish Brand vs Indian LR grade Brand 4 and Brand 1. In HPLC grade MeOH, Brand 4 had better quality than Brand 1while in LR grade, this is not the case. This means that one cannot rely on the care and quality of the manufacturer, but testing for every batch becomes mandatory (by orthogonal techniques).



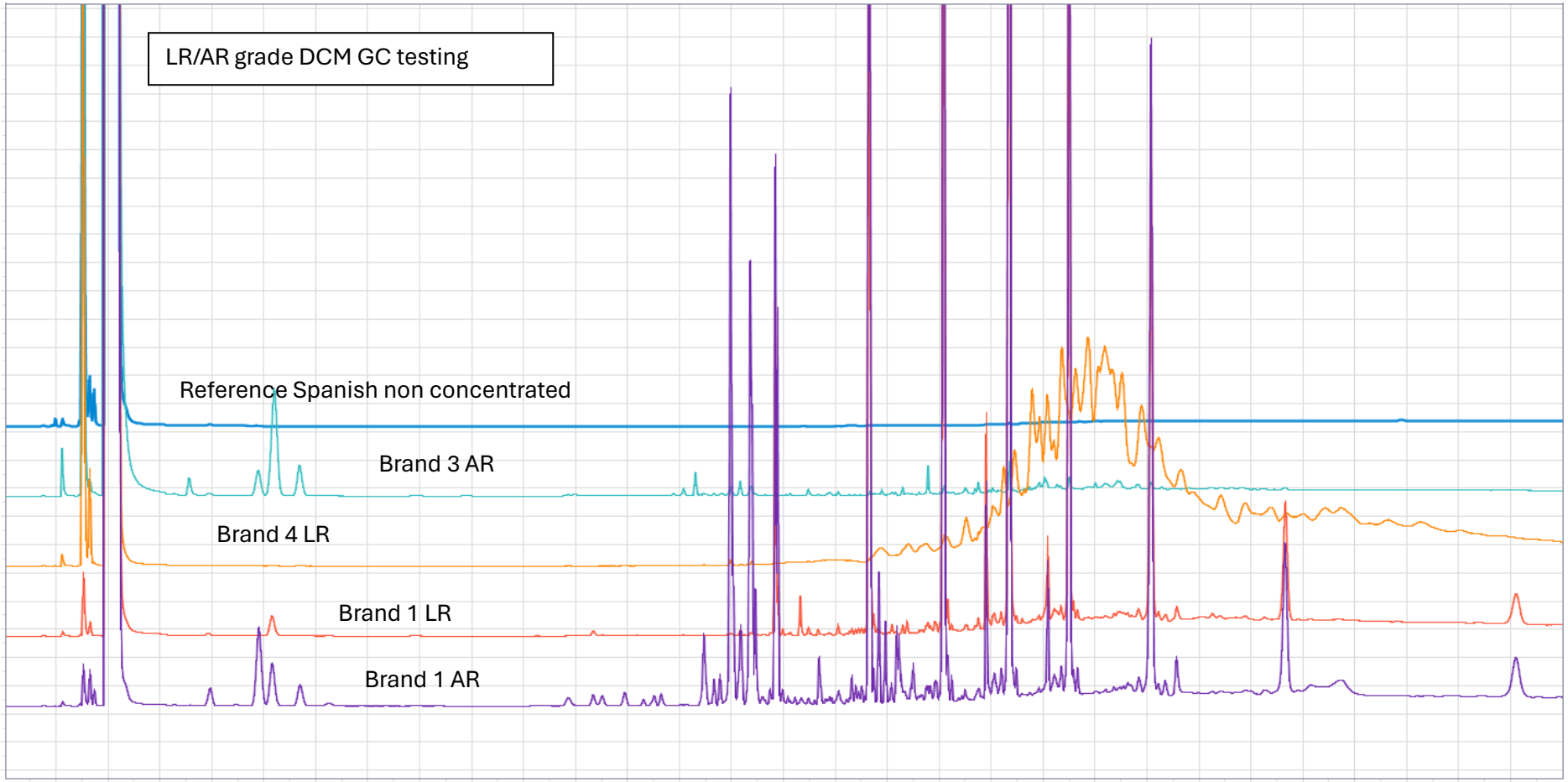
MeOH reference HPLC grade vs Brand 4 LR as compared to Brand 4 AR grade. As it can be seen in this case, there is an important difference in between the qualities of LR and AR grade Methanol.



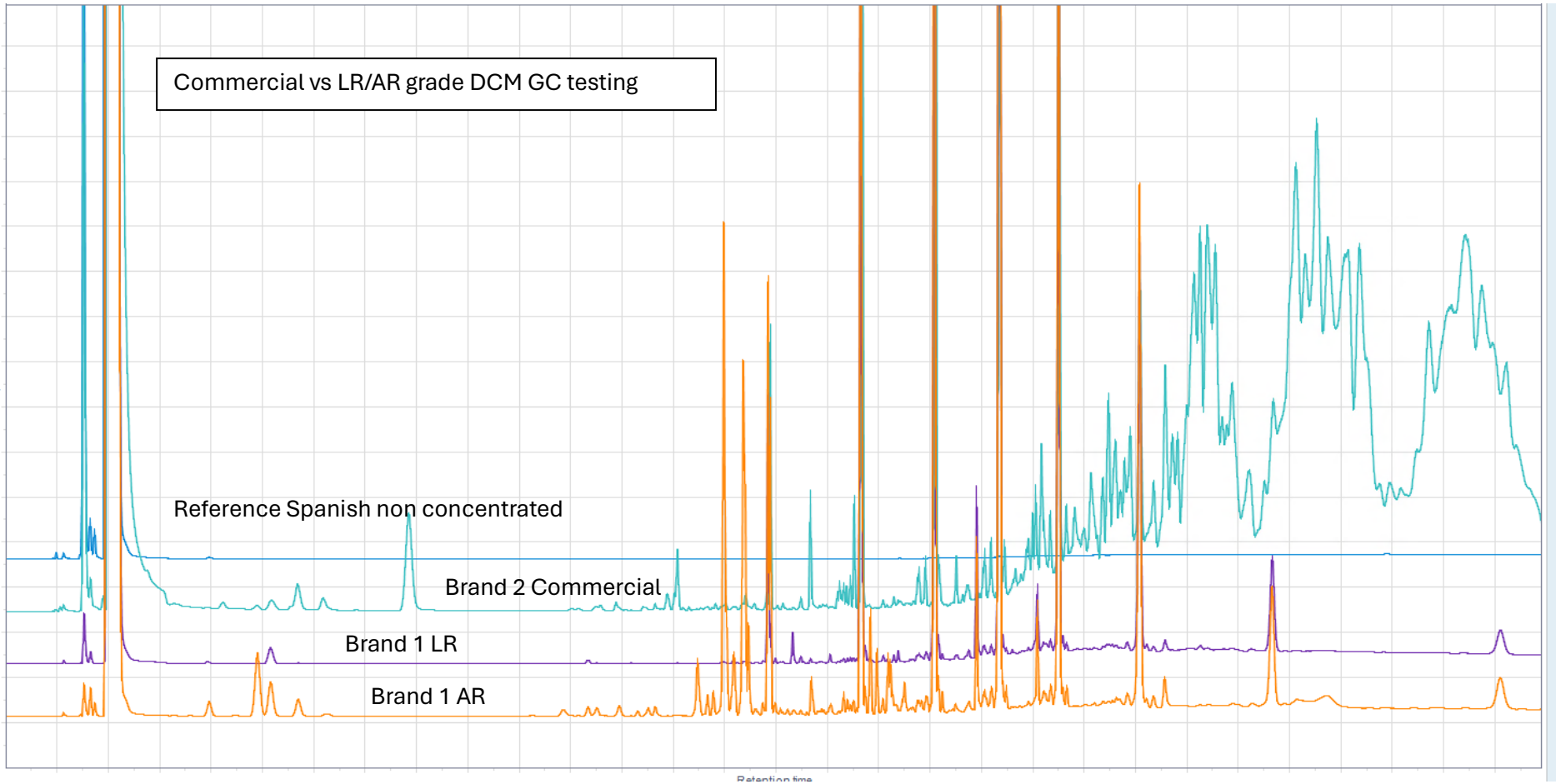
MeOH reference HPLC grade vs Brand 1 LR as compared to Brand 1 AR grade. As it can be seen in this case, there is an important difference in between the qualities of LR and AR grade Methanol also for Brand 4



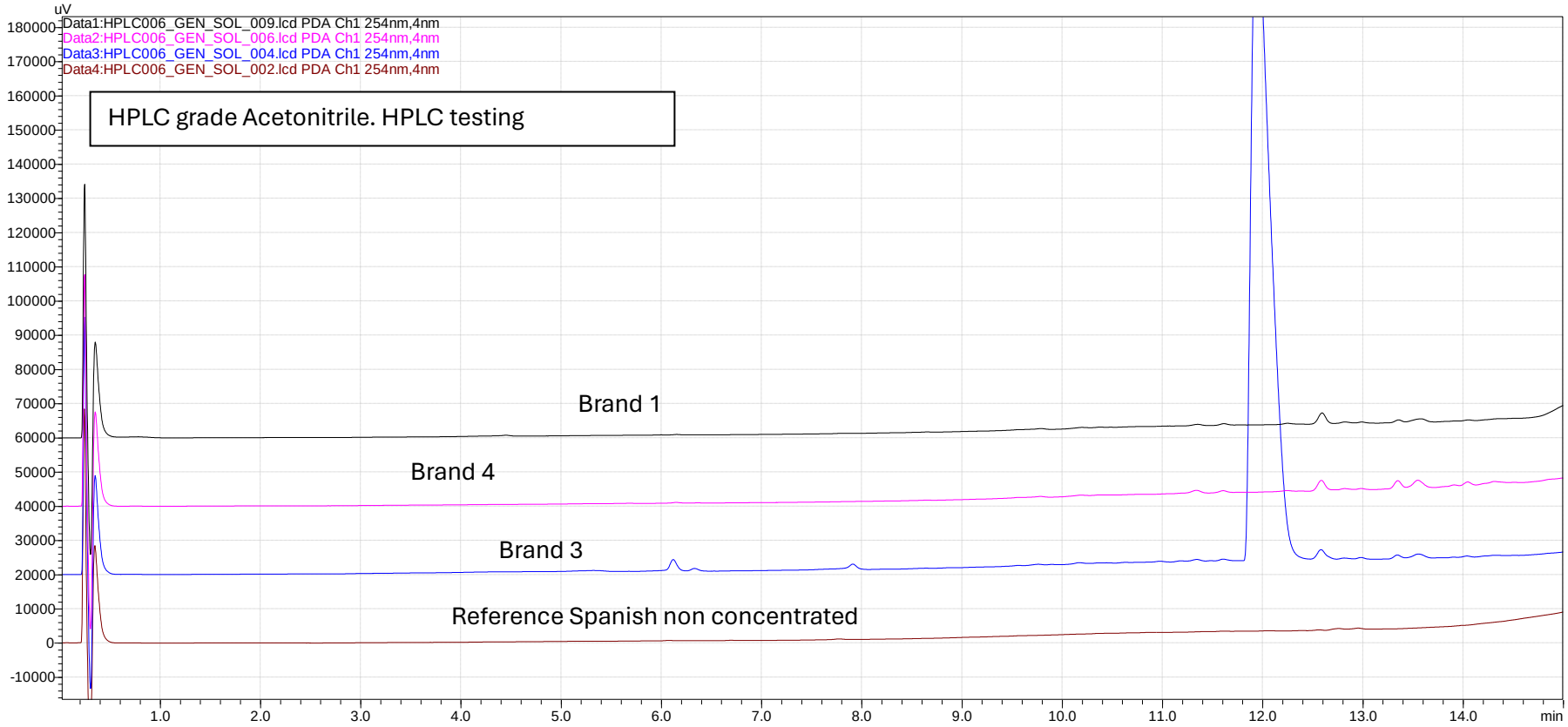
DCM (methylene chloride) HPLC spanish reference Brand vs HPLC indian brands evaporated Brand 3 vs Brand 4.



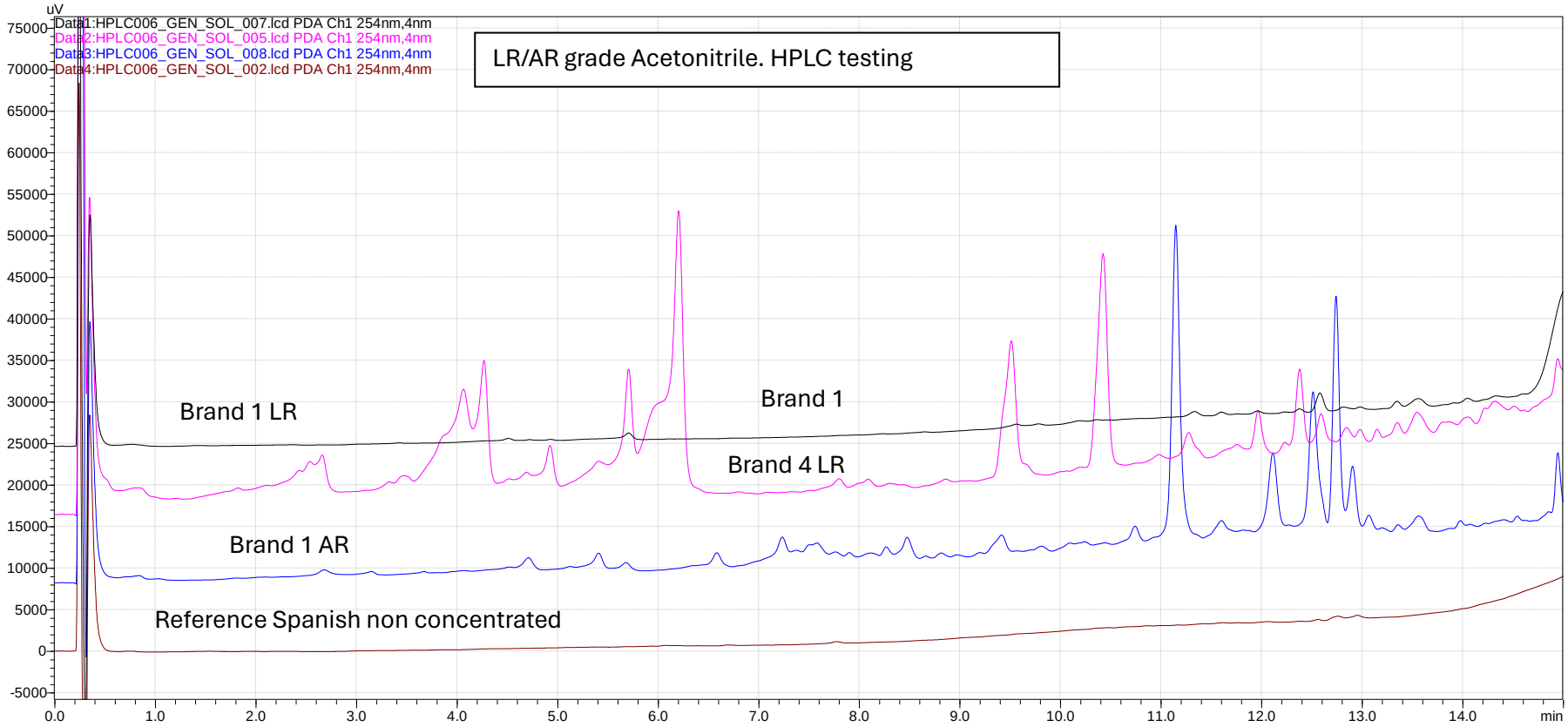
DCM reference spanih Brand, vs indian brands LR and AR grades. Brand 3 AR, Brand 4 LR, Brand 1 LR and Brand 1 AR. The best quality among those is Brand 3 AR grade. In the case of Brand 1, there is almost no difference in between LR and AR grades. Again this proves that testing cannot be avoided even when the supplier is qualified.



DCM spanish reference Brand, Brand 2 commercial grade Brand 1 LR and Brand 1AR. As one can understand, commercial solvents are our of the question for API purification.

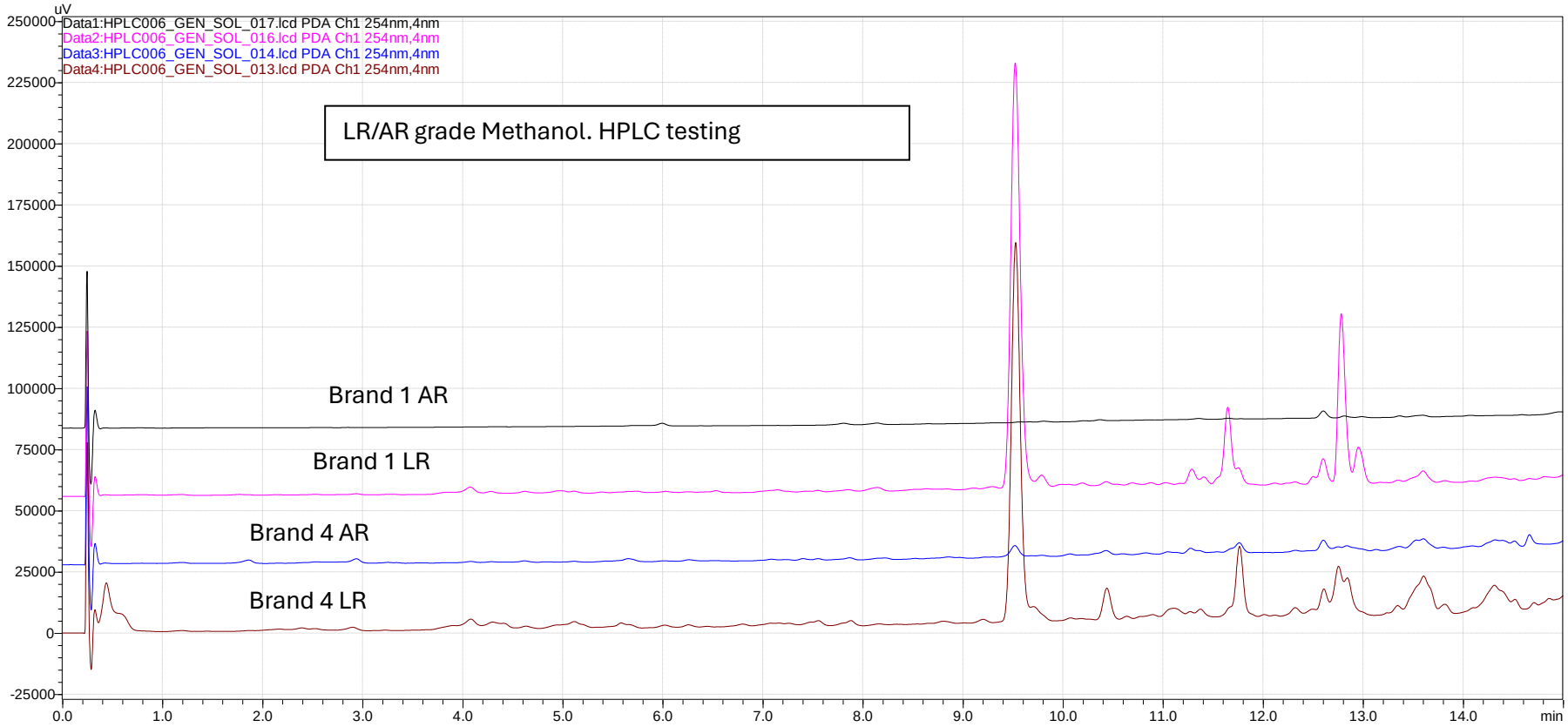


HPLC grade Spanish Brand, vs Indian brands 1, 4 and 3 all of them HPLC grade. It shows here that orthogonal testing is required because by GC the three Brands were quite similar in quality while by HPLC Brand 3 shows an important impurity that responds to aromatic wavelengths.

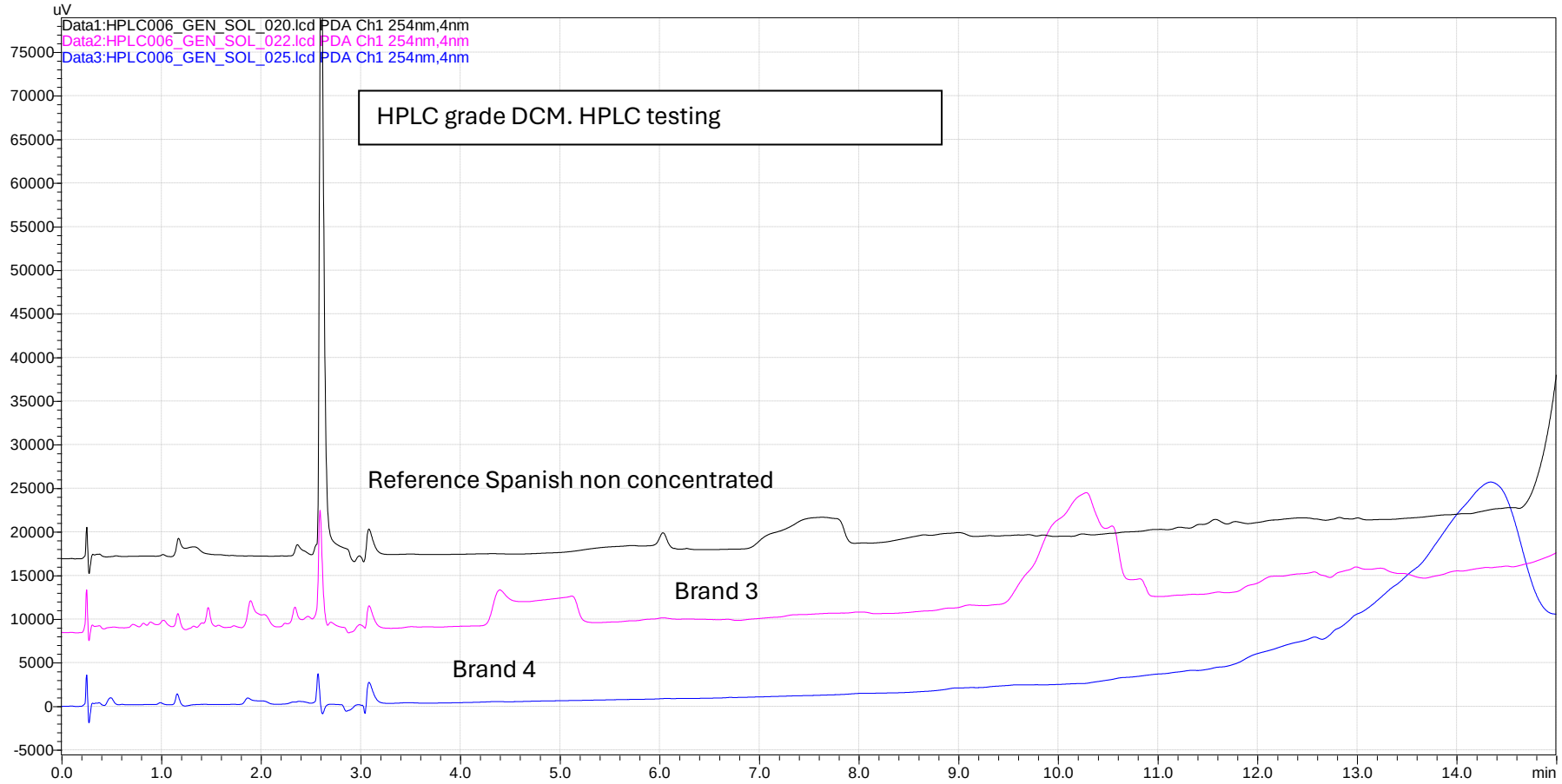


The comparison in between the reference from spanish Brand and the Indian brands 1 and 4 for LR and AR grades shows that the AR grades are not always good enough to be used in the purification (see the AR one from Brand 1).

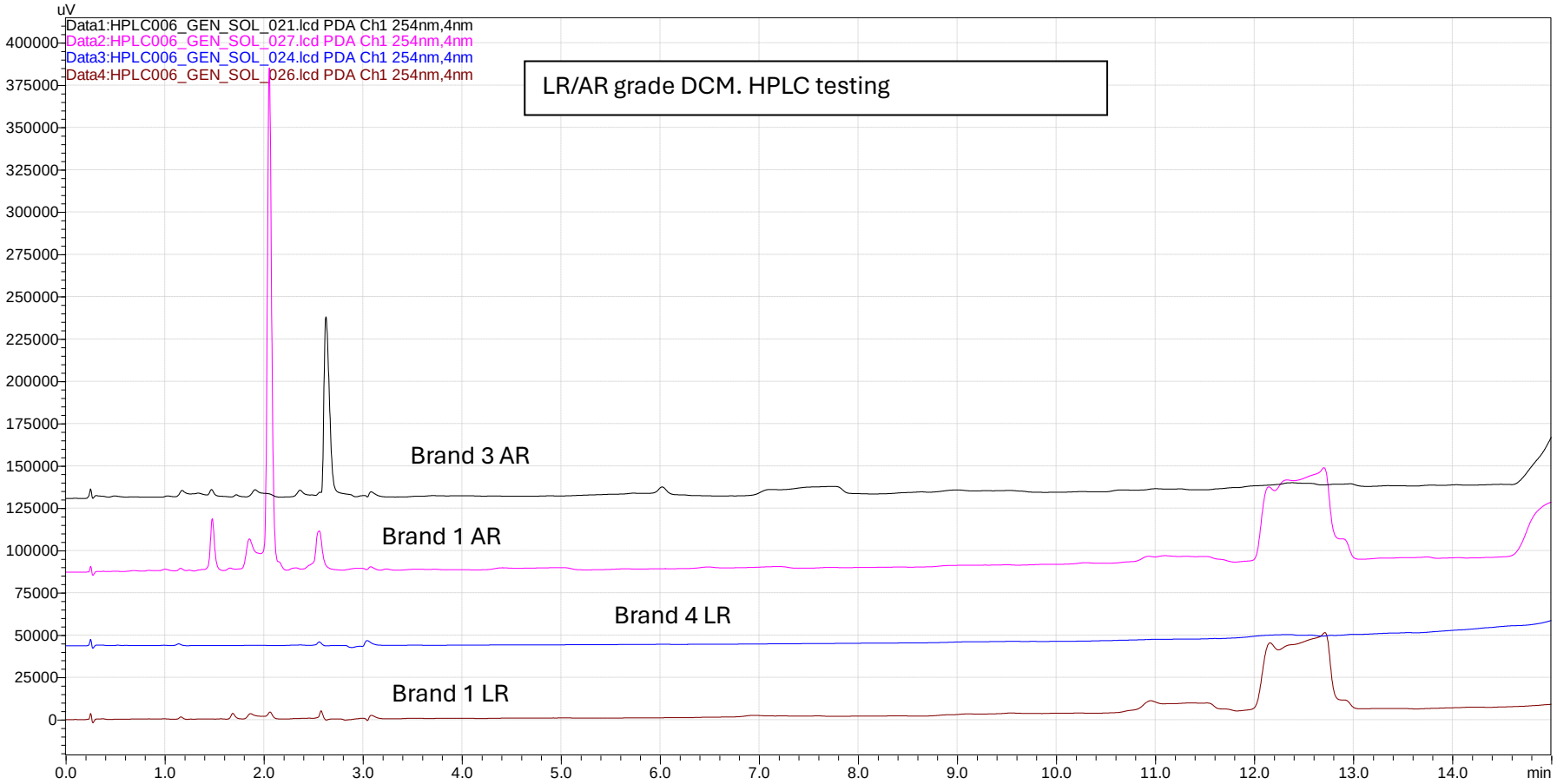
HPLC grade Spanish Brand, vs Indian brands 1, 4 and 3 all of them HPLC grade. It shows here that orthogonal testing is required because by GC the three Brands were quite similar in quality while by HPLC Brand 1 seems to be better than the other two.



Methanol LR/AR show high differences in between grades. As per HPLC both Brand 1 and Brand 4 AR grades would look good.

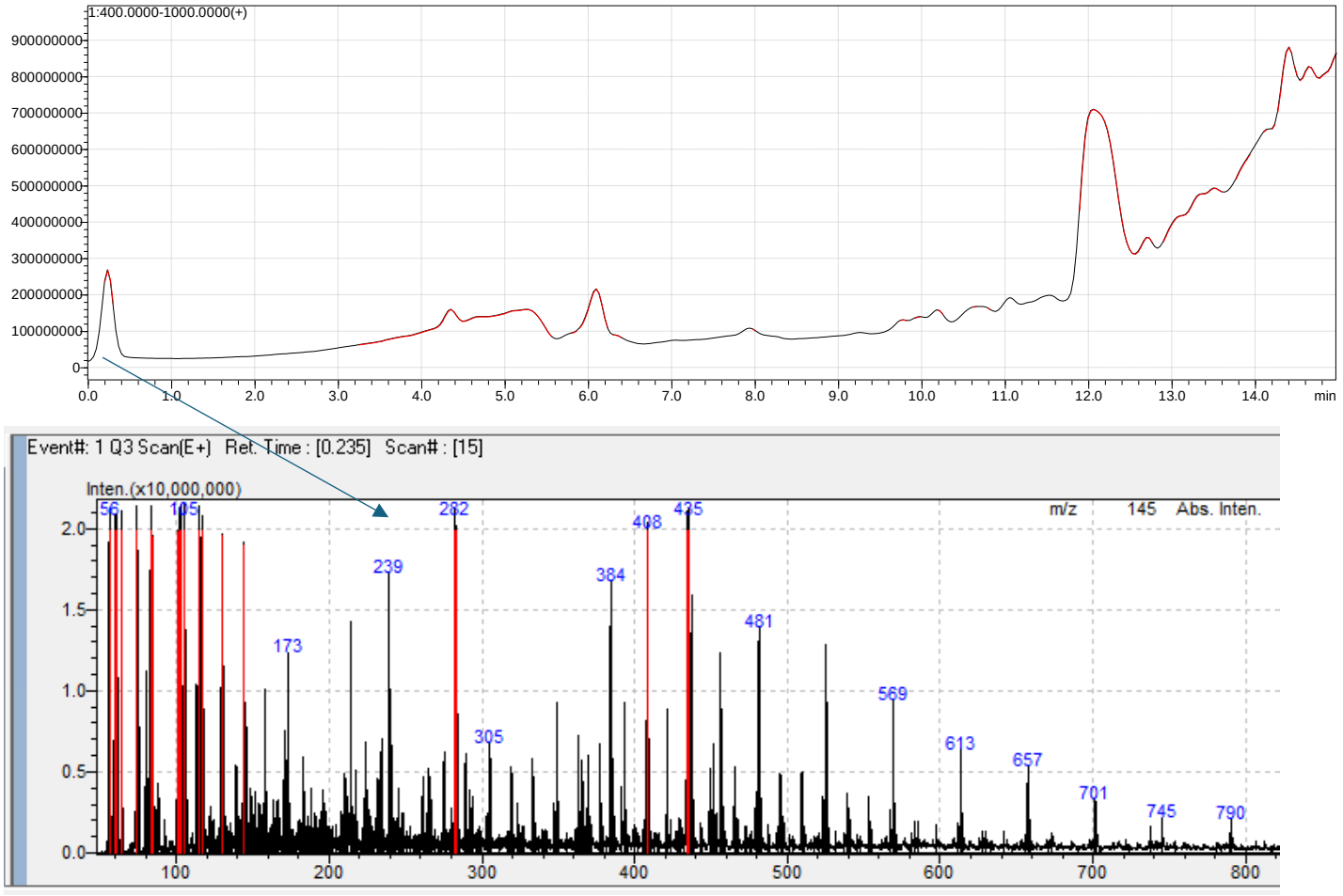


HPLC grade Spanish Brand, vs Indian brands 4 and 3 all of them HPLC grade. The indian brands both seem to have more quantity of late eluting substances.



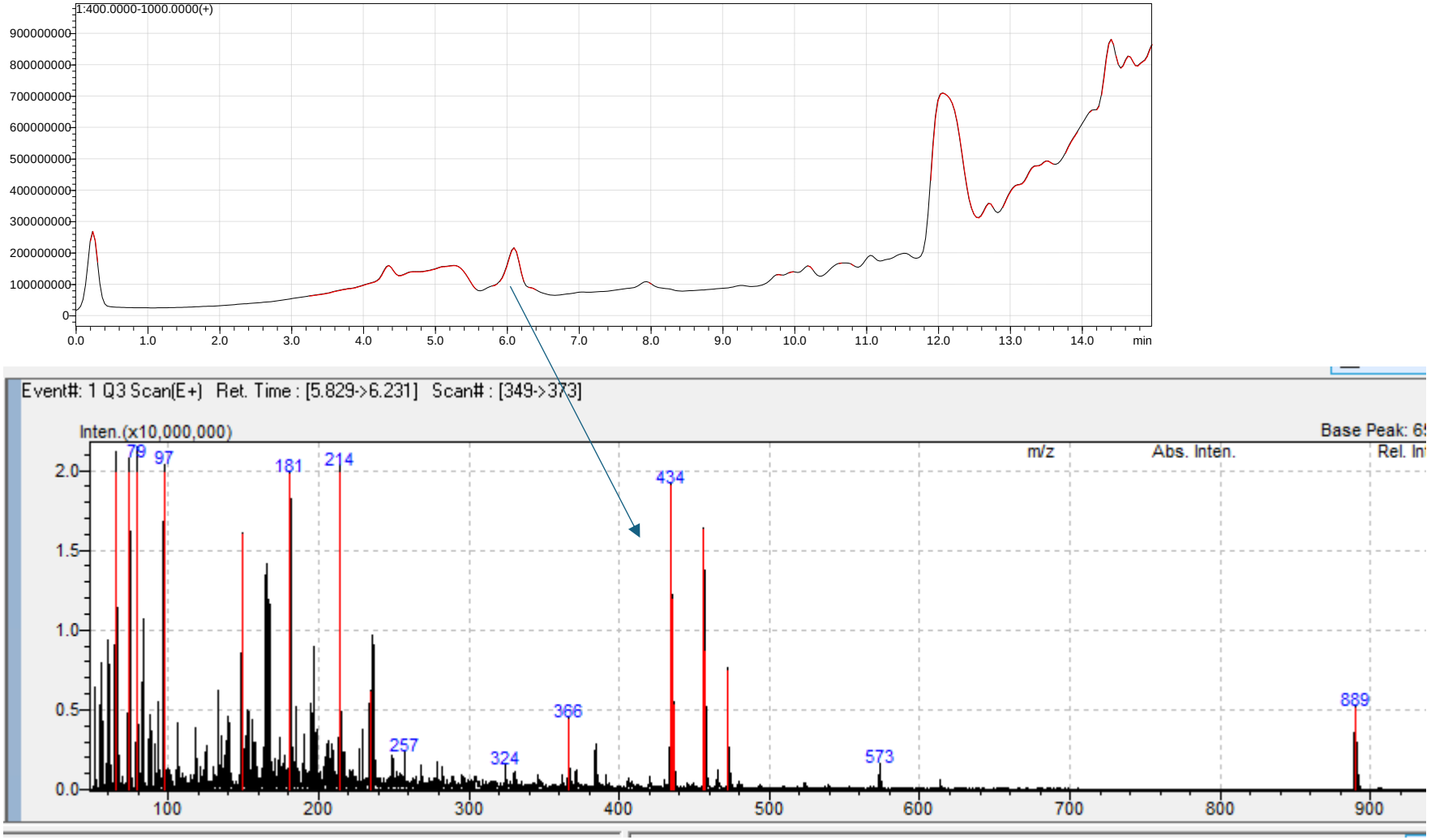
Comparison in between qualities of Indian brands 4 LR grade, 3 AR grade and 1 LR grade. The indian brands both seem to have more quantity of late eluting substances.

In the testing by LCMS not all peaks that are active on UV present ionization by ESI (+) This example of Brand 3 Acetonitrile HPLC with peaks filtered in the area from 400 to 1000.

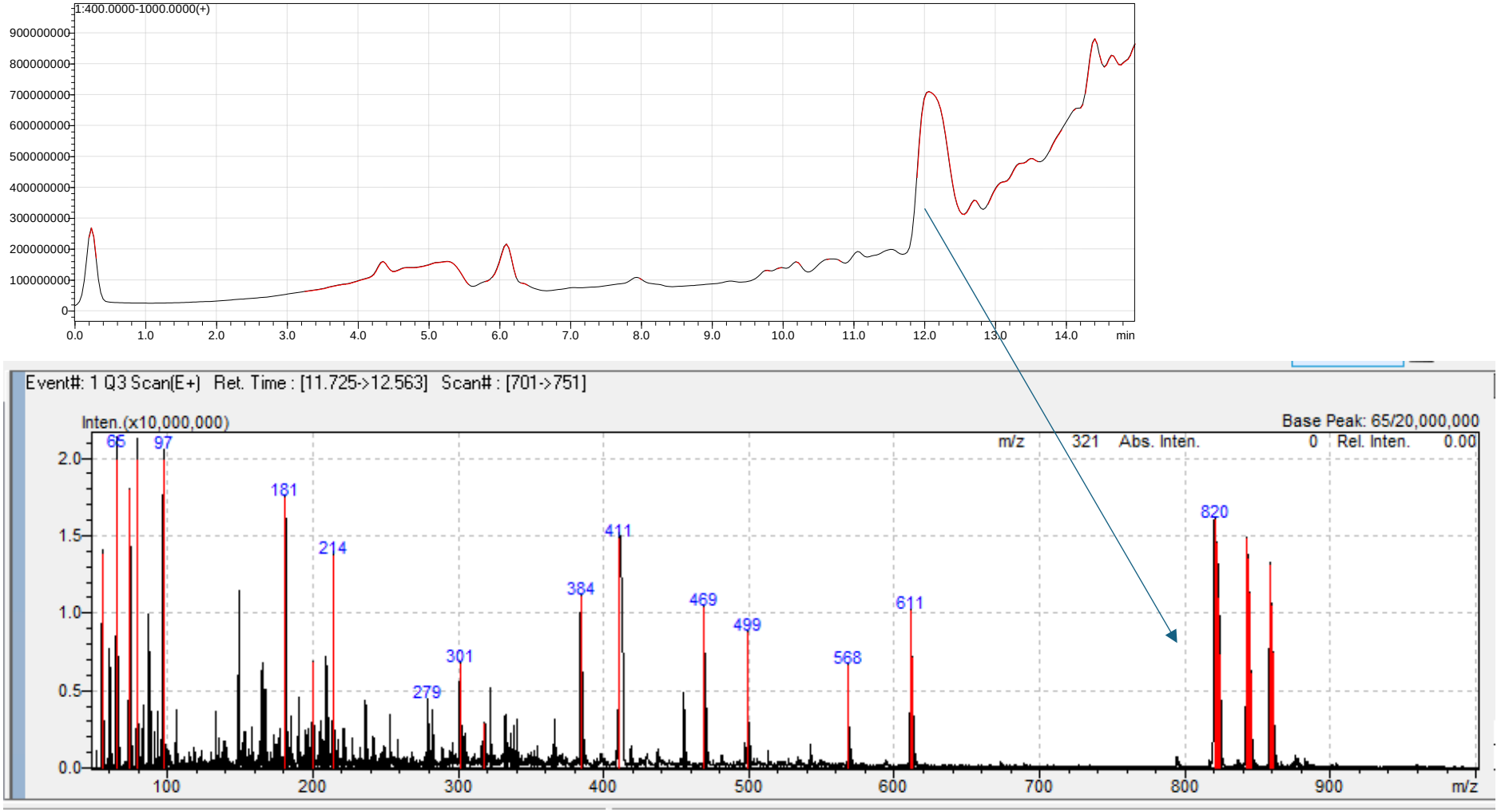


The peak eluting early shows numerous peks with polar polymeric nature.

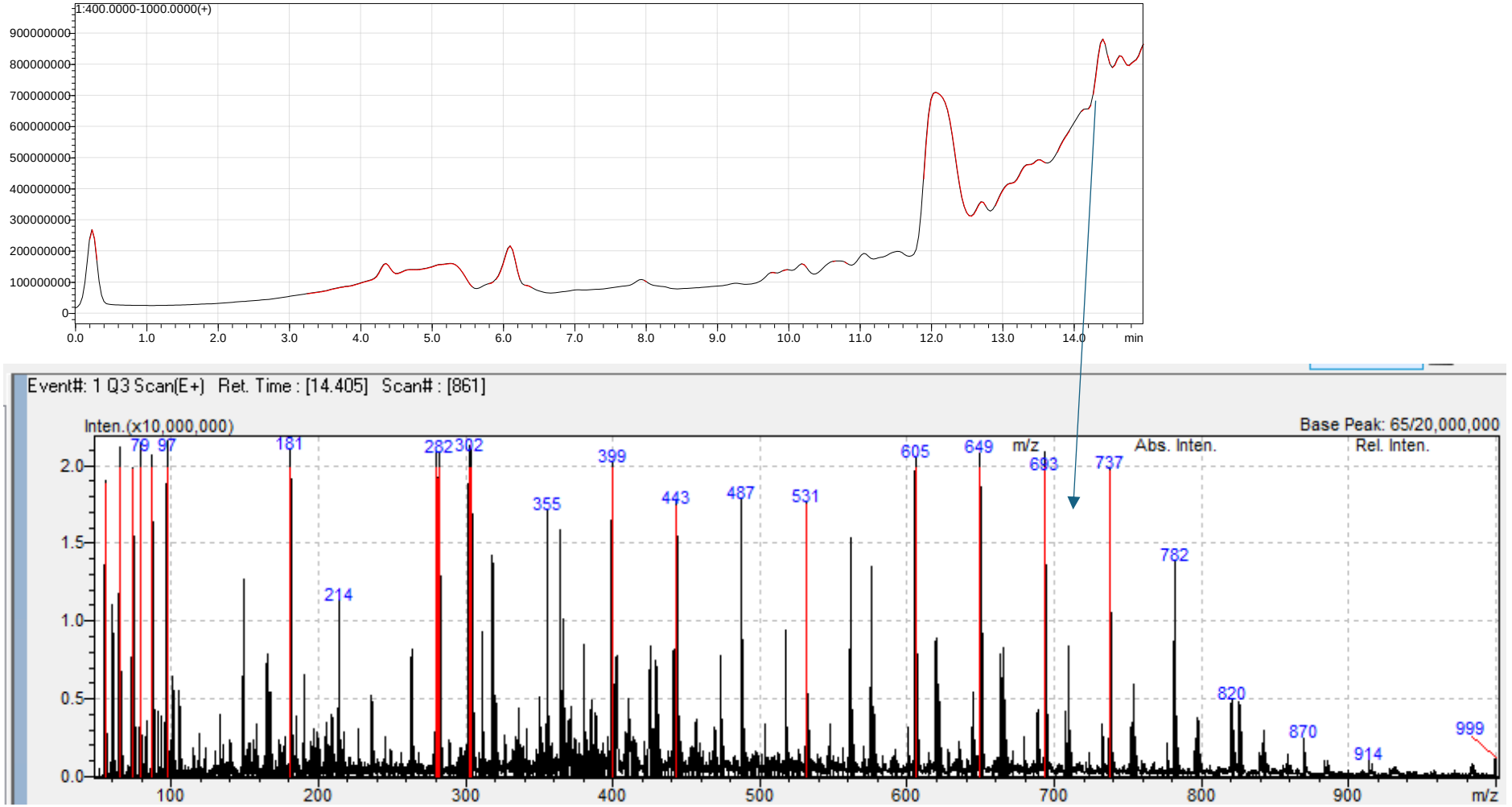
The second peak presents a substance with molecular weight higher than 400.



Again substances with molecular weight higher than 400 daltons.

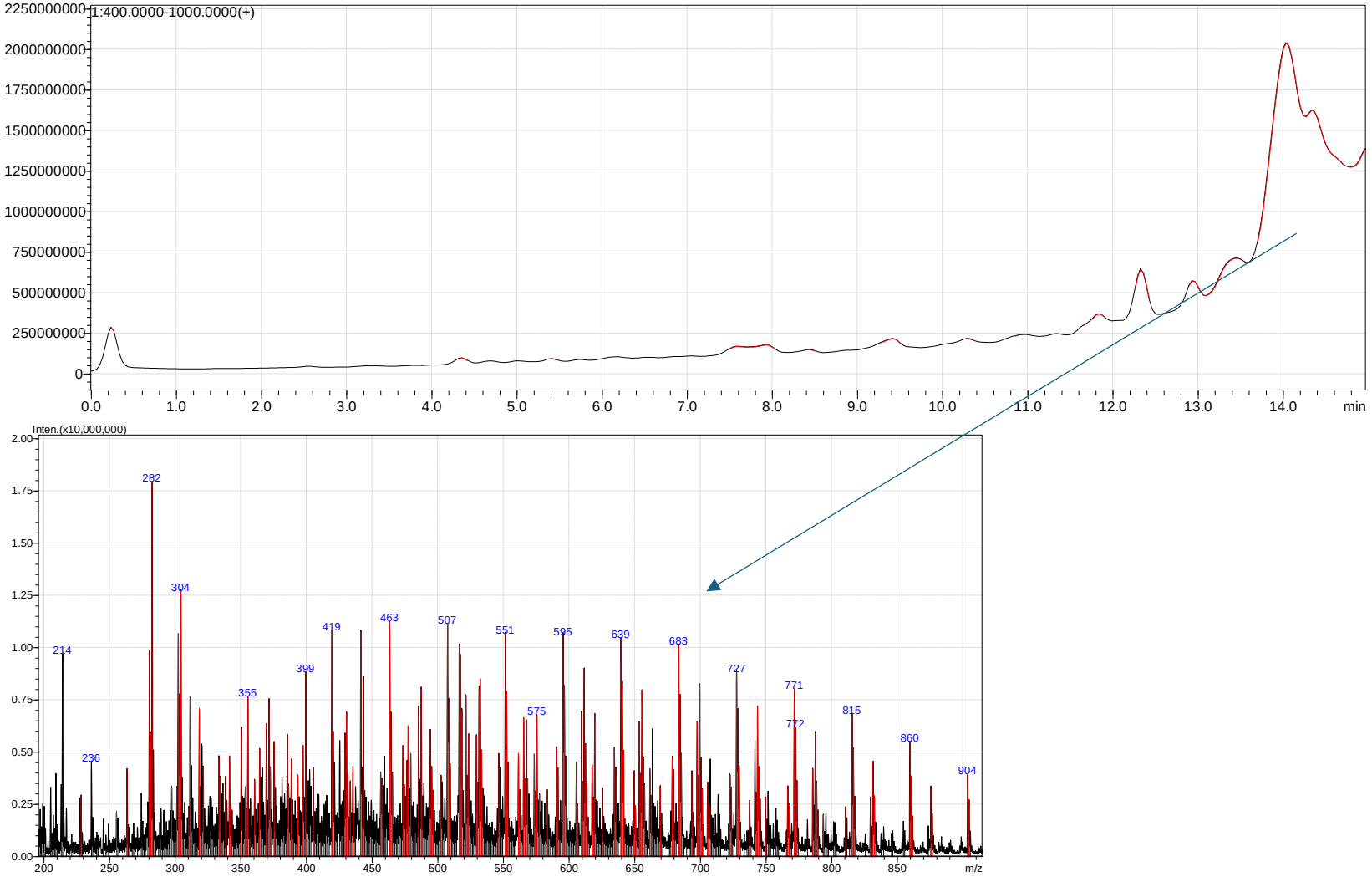


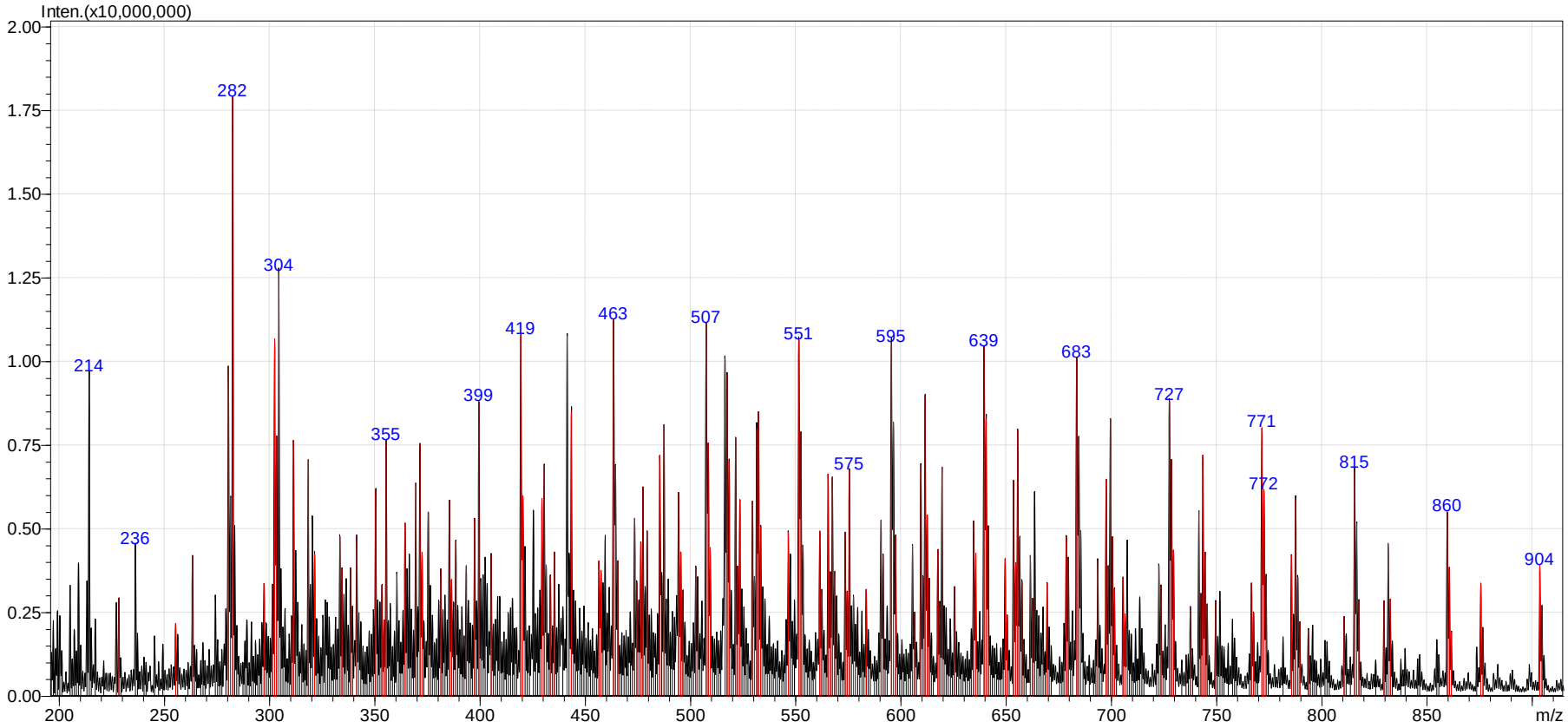
Late eluting peaks show substances with molecular weight higher than 800 daltons.



Late eluting peaks at the end of the chromatogram are clearly polymeric in nature.

The Acetonitrile LR grade from Brand 4 shows the peak at 14 minutes, which shows high intensity, contains peaks that are polymeric in nature.

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772
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860
904

8 Conclusion

Ensuring the purity of solvents used in the purification of drug substances is critical for maintaining the quality, safety, and efficacy of pharmaceutical products. It requires careful selection and monitoring of solvents, adherence to regulatory guidelines, and the implementation of rigorous analytical techniques and in house purification techniques if the suppliers are not providing the quality that is required for a particular process. Addressing solvent impurities is a key aspect of pharmaceutical manufacturing and quality control, contributing to the overall success of the drug development process.

Both the GC testing and the HPLC testing of concentrated Solutions is a good tool to evaluate and compare the purity of solvents from different suppliers. The LCMS shows a profile much ore difficult to understand because the substances do not present a high degree of ionization. LCMS is useful to understand the nature of the impurities but not to really differentiate quantitatively in between suppliers.