Getting the most out of your charged aerosol detector

Factors influencing charged aerosol detector performance

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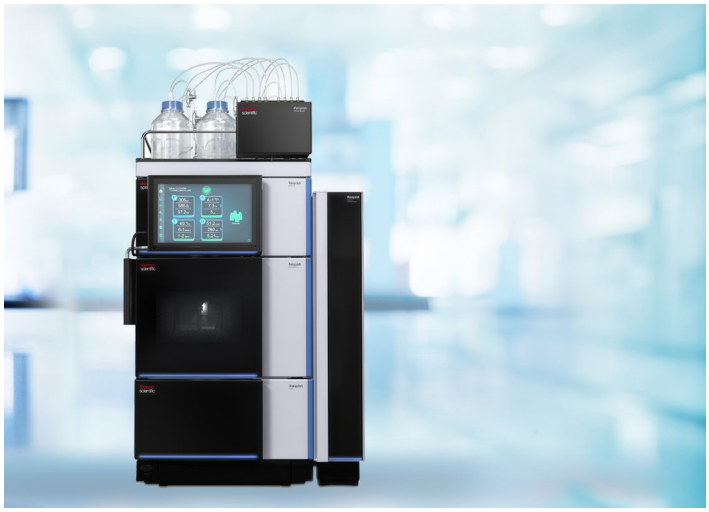

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1. Introduction

Due to its unique properties and capabilities, the charged aerosol detector (CAD) is now in widespread use and has been established as an important part of the detection portfolio of many laboratories since its introduction in 2004. Given the high sensitivity and underlying working principle, which in general shows greater similarity to mass spectrometers (MS) than the ubiquitous optical detectors that are mainly used with high performance liquid chromatography (HPLC), there are some fundamental differences in the proper handling of the CAD compared to traditional HPLC detectors.

The first part of this technical guide describes the various factors that affect the performance of the CAD. The second part focuses on practical considerations and shares tips, tricks, and best practices for operating the detector.

Note: Using this guide does not replace reading the manual.

2. Part A. Factors to consider when using the CAD

2.1 Scope of detection

The ability to predict whether charged aerosol detection can measure a particular analyte is of considerable interest. The CAD's response for a given analyte is primarily determined by its volatility specifically as it relates to aerosol evaporation. In addition to properties such as boiling point and vapor pressure, the influence of evaporation temperature and the effect of mobile phase additives on the response of ionic analytes are main considerations. Analytes that behave as non-volatiles give similar uniform response, as shown in Figure 1. See Thermo Scientific Technical Note: 72806: Charged aerosol detection - factors affecting uniform analyte response[1] for greater details.

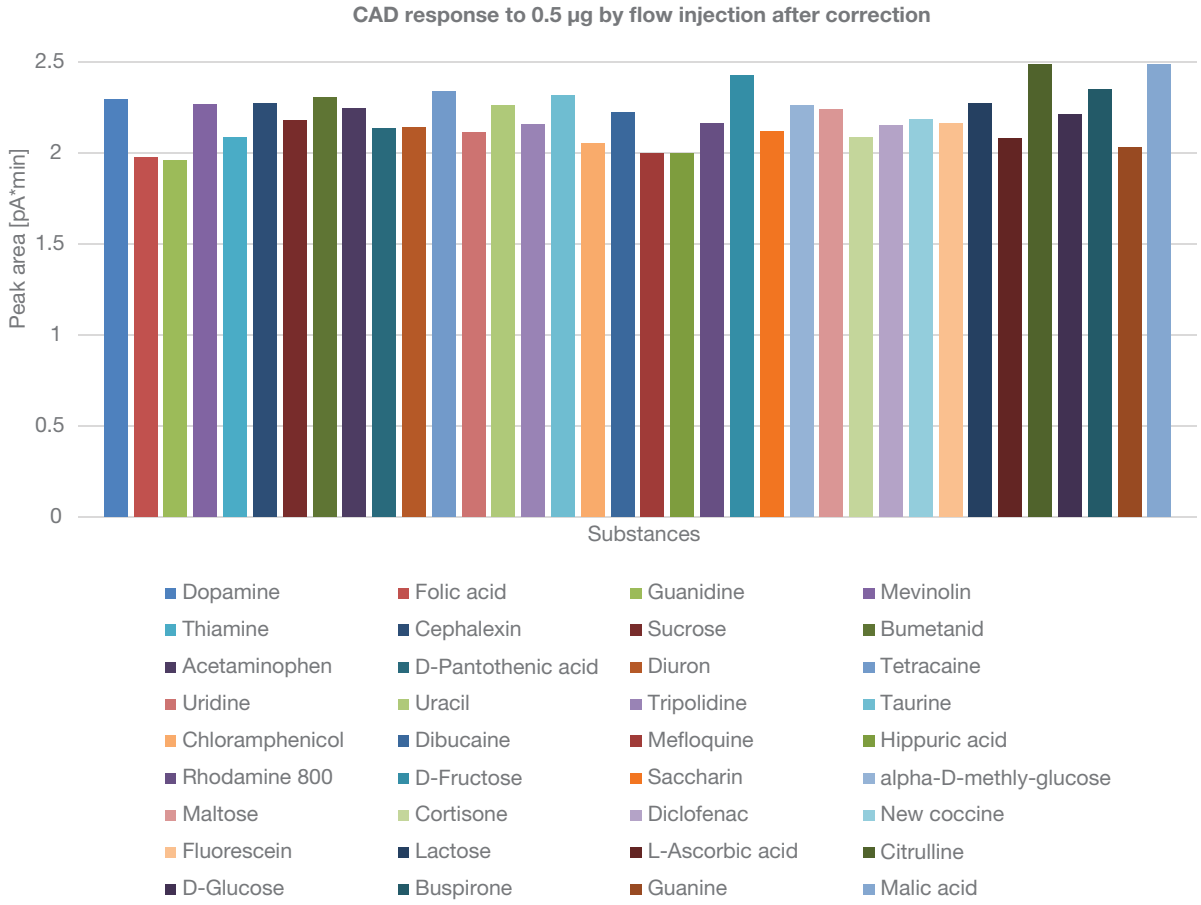


Figure 1. Uniform response of charged aerosol detection for a range of chemically diverse test substances using flow injection analysis (FIA) (0.5 µg into a mobile phase stream of water/acetonitrile 20/80 (v/v)). For further details refer to Technical Note 72806: Charged aerosol detection - factors affecting uniform analyte response.[1]

Analytes that behave as semi-volatiles, however, will show non-uniform response due to their reduced signal, especially at lower injected mass levels. Analytes that behave as volatiles show little or no response. Several studies have described approximate cut-offs beyond which all analytes behave as non-volatiles. For example, one study of a large and diverse compound library showed that any substance with a boiling point (BP) above 400 °C was found to behave as a non-volatile.[2] Another similar study showed that any analyte with both an enthalpy of vaporization above 65 kJ/mol and a molecular weight above 350 g/mol behaved as a non-volatile.[3] Similar cut-offs have also been described in relation to vapor pressure. It should be noted that these described cut-offs were obtained using the instruments' default conditions. A key instrumental setting is the evaporation temperature (T_{Evap}) where a higher or lower set temperature will shift, for example, a BP cut-off to higher or lower values, respectively.

The underlying process of spray-drying is also not fully explained by these volatility parameters alone. Thus, for analytes with values beyond a given volatility limit (e.g., BP < 400 °C) there may be unexpected outliers and differences in sensitivity between analytes. For example, while there can be high confidence that all analytes with a BP > 400 °C will behave as non-volatiles under default conditions, an analyte with a BP of 150 °C may behave as a non-volatile while one with a BP of 350 °C may behave as a semi-volatile. In this regard, a main factor that influences response is whether the analyte elutes from the column as an ionic solute. In these cases, an inherently volatile or semi-volatile charged analyte may form a less volatile salt with an oppositely charged species. This most often occurs between ionic analytes and mobile phase additives, which are often present at much higher concentrations within the initial droplets formed by nebulization. As an example, the chloride ion will behave as a volatile analyte (forming volatile hydrogen chloride) when there is no mobile phase additive but will behave as a non-volatile when ammonium is present (forming non-volatile ammonium chloride) as an additive.

2.2 Performance parameters

Baseline noise, drift, and background current are very useful parameters to monitor during method development, routine use, and for troubleshooting.

2.2.1 Noise and drift

Baseline noise is a well-known parameter to every chromatographer and refers to short-term fluctuations in baseline signal usually of higher frequency than the chromatographic peaks. Noise is often one of the parameters determining performance of chromatographic methods, as the limit of detection and limit of quantitation are defined as multiples of the ratio of an analyte's signal to the average background noise. Consequently, chromatographers are keen to identify the various sources of baseline noise and minimize the noise by proper selection of experimental conditions. While most chromatographers are well-versed in identifying and providing a remedy for a noisy baseline with optical detectors, the sources of noise for a CAD typically have a different root cause. This results from the fundamentally different working principles and selectivity of charged aerosol detection compared to optical detectors.

Drift refers to longer term changes in baseline signal, such as over the course of a chromatographic run or the course of an analytical sequence. In most cases, a drift over the course of the sequence can usually be attributed to the hardware (e.g., when operated at non-equilibrated conditions) or laboratory surroundings (e.g., a non-thermostatted laboratory). Whenever gradients are used, it is common to observe a (reproducible) drift within a chromatographic run that can usually be attributed to differences in the physicochemical properties of the mobile phases. Unlike baseline noise, the drift does not have a direct impact on the derived performance parameters. Most of the time drift and noise are correlated.

Both noise and drift are performance parameters which are routinely evaluated by any modern chromatography data system (CDS) and suitable, device specific, limits under defined conditions are provided by any instrument manufacturer. These values and conditions, together with suitable templates (e.g., in the form of a performance qualification) can help in evaluating and troubleshooting a device's performance.

2.2.2 Background current

The CAD is a universal detector that provides a signal proportional to the amount and size of particles generated during a spray-drying process. Particles are formed whenever a non-volatile or semi-volatile substance is

present, irrespective of its exact chemical nature. Even under the best achievable conditions, there is always some semi- or non-volatile material present. This can be seen in Figure 2 where the dried aerosol of a Thermo Scientific™ Corona™ Veo™ RS Charged Aerosol Detector was analyzed with respect to number frquency (number of particles per second) and mean size (geometric mean diameter of a log-normal size distribution) of particles formed. As shown in Figure 2A, even when a mixture of highly pure methanol and water is forming the spray, a large number of particles (>10^9/s) are formed. This is not unexpected considering the typically >100 ppb levels of nonvolatile impurities in highly pure solvents as reflected by their residue after evaporation specification. With the addition of a non-volatile substance, e.g., theophylline, the number of measurable particles as well as the mean size of the generated particles increases, as can be seen Figure 2B and C.

The generated particles subsequently make up the detector signal. As the CAD is measuring the charge accumulated on the aerosol particles per time unit, the resulting signal is an electric current. The signal generated by the CAD in the absence of additional analyte is referred to as background current. The background current is therefore a reference signal generated by the total amount of semi-volatiles and non-volatiles entering the detector. An increase in background current usually leads to a higher noise level being observed. This makes background current a more useful parameter to measure than noise when troubleshooting charged aerosol detectors, as it is independent of some method settings (e.g., data collection rate, filter constant) and can help differentiate between hardware related issues (e.g., pump noise, electronic noise) and an excessive amount of semi-volatiles and non-volatiles (e.g., stemming from impure solvents or additives, contamination of the system, etc.).

The presence of semi-volatile and non-volatile impurities during a chromatographic analysis is almost always found to be the limiting factor for method performance. To ensure optimal performance and consistent results, it is necessary to identify sources of these impurities and develop strategies to minimize their introduction and interference with the chromatographic analysis.

2.3 System setup and configuration

2.3.1 System setup

Before connecting the CAD to any HPLC system, it is important to consider whether the system has been previously used with mobile phases containing non-volatile additives, e.g., phosphate buffers or non-volatile ion pairing reagents. If so, then an extensive flush of the system with suitable solvent(s) prior to use with the CAD is required. It may also be necessary to exchange wetted parts of the system that can retain these non-volatiles as they may have a “memory effect” (i.e., slowly and persistently releasing semi- and non-volatiles that have been incorporated during previous usage, resulting in baseline disturbances, noise, and higher background current). Typically, this means exchanging the solvent lines and inlet frits, but in cases of severe contamination the exchange of other components such as the degasser cartridges may also be warranted.

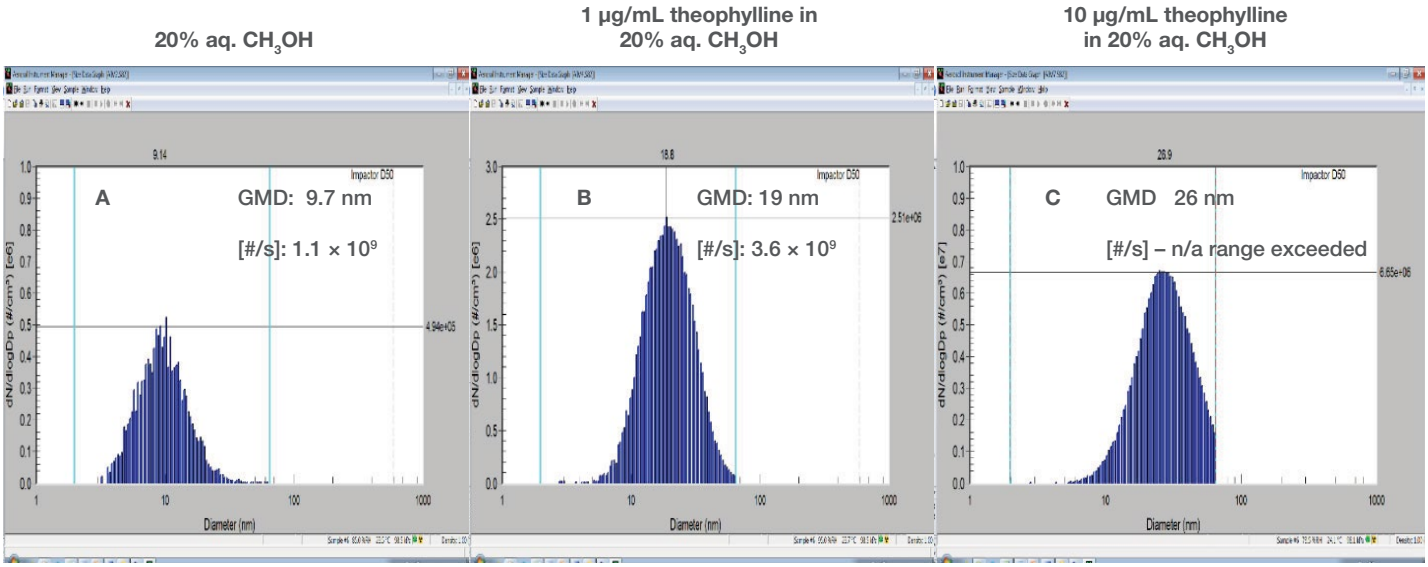


Figure 2. Scanning Mobility Particle Sizer (SMPS) spectrometer, TSI Model 3938, TSI, Inc. 1.0 mL/min flow; Corona Veo RS; GMD = geometric mean diameter; [#/s] = number of particles per second

In many system configurations, the CAD is used in combination with an optical detector like a variable wavelength detector (VWD) or diode array detector (DAD). As the CAD is a destructive detector, it must be the last detector in the flow path and therefore downstream from an optical detector. When the CAD is used in conjunction with optical detectors whose flow cells have a lower pressure rating (e.g., Thermo Scientific™ Vanquish™ LightPipe™ flow cell-based DAD, fluorescence detector, or refractive index detector) the backpressure must be considered. This is especially true when an additional stream-switching valve (e.g., as part of the Corona Veo RS) is being utilized between the CAD and the optical detector flow cell since pressure pulses can occur when the valve position is switched. The pressure requirements can necessitate the change of some of the capillaries connecting the optical detector(s) to the CAD and/or stream-switching valve in order to avoid exceeding the pressure rating and thus damaging the flow cell(s). As the use of larger inner diameter capillaries comes at the expense of increased dispersion, balancing the generated backpressure and dispersion is unavoidable. Whenever flow cells of lower pressure rating are utilized in multi-detector setups, the use of inline overpressure relief valves is highly recommended. Indeed, they should be used with any analytical system where the flow cell pressure rating may be accidentally exceeded.

2.3.2 Flow splitting

Due to the advantages of complementary detection techniques leading to more holistic information about a sample, the CAD is often not only used together with one or more optical detectors, but with a MS as well. For example, see Thermo Scientific Application Note 72869: A multi-detector platform comprising UV/Vis, charged aerosol and single quadrupole mass spectrometric detection for comprehensive sample analysis.[4] As the CAD and MS are both destructive detectors, the mobile phase flow must be split between the two detectors. For systems using both CAD and MS, an additional optical detector like a VWD or DAD must be located post column, but prior to the flow splitter to avoid loss of sensitivity (Figure 3). Three different types of flow splitters are available, differing in their accuracy, flexibility, ease of use, and cost.

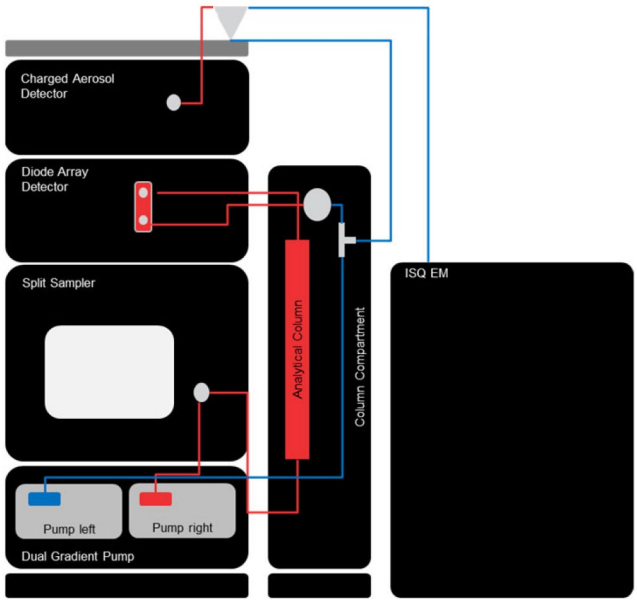


Figure 3. Multi-detector set-up with flow splitting (triangle)

Tee flow splitters have the flow split ratio determined by the backpressure generated by connected capillaries and devices for each flow path. The split ratio must be determined and optimized through flow rate experiments to achieve the desired flow split.

Static flow splitters have a fixed split ratio that can be modified by replacement of a flow cartridge. The cartridges use fluid resistor technology to create a given split ratio. The volumes in the splitter are also adjusted as to avoid a change of split ratio during gradient elution. Static flow splitters are limited to popular static flow ratios (e.g., 1:1, 1:2, 1:5, 1:10). As long as the hydrodynamic resistance, i.e., backpressure, of the splitter is large compared to the connected capillaries and devices, they provide a very accurate and constant split ratio.

Adjustable flow splitters work like static flow splitters but differ in that they offer adjustable hydrodynamic resistances within a specific flow split ratio range (e.g., 1:1–1:20). Flow cartridges are available in specific flow split ratio ranges for increased flow accuracy.

For accuracy and convenience, it is recommended that either fixed or adjustable flow splitters be used as they have built-in fluidic resistors to minimize the changes in eluent viscosity during solvent gradients. Be aware though that they require the introduction of a large backpressure in the flow path, which limits the choice of columns and flow rates, and prohibits the use of optical detectors with a lower pressure rating.

2.3.3 Post-column addition

In several cases, post-column addition of solvent is beneficial when a CAD is used. The CAD response for non-volatiles is independent of chemical structure but is dependent upon mobile phase solvent composition. For example, analytes that elute at different times during solvent gradients may have different response factors due to changes in eluent viscosity and surface tension. To minimize this gradient effect on response it is typical to use inverse gradient compensation, so the CAD always "sees" mobile phase of constant composition. For an in-depth review see: TN 73449: Why use charged aerosol detection with inverse gradient?[5] Briefly, this approach uses a second pump to deliver a solvent gradient that is the exact opposite of the analytical gradient. The solvent streams are combined post column using a tee connector. Thus, the CAD receives mobile phase of constant composition, typically, at the midpoint of the gradient but at twice the flow. This approach not only improves response uniformity, but also provides a more stable baseline. A practical consideration when using this approach is to ensure that the analytical gradient and inverse gradient are synchronized and any differences in flow path volume and timing are minimized. These requirements can easily be addressed with the Thermo Scientific™ Vanquish™ Duo for Inverse Gradient, providing a UHPLC capable system equipped with the Thermo Scientific™ Vanquish™ Dual Gradient Pump, an appropriate tubing kit and easy to use wizards in the Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) 7.3.

Another use for post-column addition is to improve sensitivity. This may result from two effects. The first is dilution of impurities in the column eluent by addition of a cleaner solvent. The second is from the increased analyte mass transport to the detector by the isocratic addition of a lower viscosity (lower surface tension) solvent after the column.

In all cases it is mandatory to make sure that: a) solvents are completely miscible, and b) analytes, matrix components and additives remain fully soluble. Furthermore, the total flow of solvent to the CAD must not exceed its upper limit, otherwise inadequate solvent evaporation can lead to characteristically irregular baseline noise and, in a worst-case, flooding of the detector.

2.3.4 Gas supply and ventilation

The CAD requires a constant gas supply pressure of 4.8 bar (70 psi) with a maximum supply pressure of 6.2 bar (90 psi), and typically uses 4 L/min of nitrogen gas. The gas needs to be free from water vapor, hydrocarbons/oil vapor, and particulates (>0.1 µm). The use of an inline filter to condition the incoming gas is recommended. While pressurized air can be used with a CAD as long as solvents are not highly combustible, nitrogen gas is highly recommended. For solvents that can form highly combustible or explosive mixtures (like tetrahydrofuran (THF)), it is mandatory to use nitrogen gas of 99% purity. There are three common approaches for supplying nitrogen gas:

Cylinder/tank: readily available in nearly every laboratory, is very safe, maintenance-free, and convenient to use. Nitrogen is pressurized at around 200 bars in a steel cylinder, so an output gas regulator must be used to reduce the incoming gas pressure to meet the requirements of the CAD. The filling volume of gas cylinders commonly used in the laboratory is around 9.5 m^3, which corresponds to approximately 40 hours of continuous CAD operation. This approach suffers from frequent operational interruptions as the output pressure must be regularly adjusted as the cylinder empties, and cylinders must be replaced when emptied. This option can be expensive in the long run. For practical consideration, the operator must remember to open the valve prior to connection to the CAD to remove any debris which may be present in the tubing.

Dewar: liquid nitrogen in an insulated container, which uses ambient energy to evaporate part of the liquid nitrogen and thus generate pressurized gaseous nitrogen. These tanks typically require adjustment of the pressure building valve to achieve elevated and/or maintain a specified output pressure. A 50 L dewar can deliver nitrogen for up to approximately 140 hours of operation, requiring less frequent interruptions and is typically less costly than gas cylinders. Liquid nitrogen, even more so when pressurized, poses a laboratory safety hazard and appropriate precautions need to be taken.

Generator: many laboratories use generators that produce high-purity nitrogen by passing pressurized air through a bundle of fibrous semipermeable membranes. Nitrogen generators are available in various sizes, some can even supply whole buildings, while others are designed to supply a single instrument. Similarly, the pressurized air can be provided by either a centralized in-house source or a local compressor dedicated to a single nitrogen generator. Nitrogen generators provide a stable, safe, and easy to use source of high-quality nitrogen. While the initial cost is high compared to other solutions, the running costs are very low, and interruptions usually only occur due to a scheduled annual maintenance.

If a nitrogen supply is used with multiple instruments or for servicing a complete laboratory, make sure that the recommended pressure and flow ratings for the CAD are met even during times of maximum nitrogen consumption. When splitting flow from a large format generator to a CAD, it may be necessary to install an upstream gas regulator to ensure compatibility with other instrumentation. A suitable modular stand-alone combination tuned to the needs of the CAD is available.

The gas exhaust from the CAD may contain hazardous components and must be connected to a ventilation system to safely remove the exhaust from the laboratory. Avoid connecting the gas exhaust to strong negative or pulsating pressure ventilation systems since this may result in unstable pressure within the CAD leading to reduced performance. Do not attach an active exhaust pump to the CAD exhaust.

2.4 Sources of noise and drift

For optimal performance, levels of non-volatile and semi-volatile impurities in the mobile phase stream entering the CAD should be kept to a minimum. There can be multiple sources of impurities including general lab equipment, the HPLC system, mobile phase components, and column bleed.

2.4.1 General lab equipment

Laboratory glassware is a common source of non-volatile contaminants. This can include components that leach from the glass over time, left-over residue from prior use, or from cleaning detergents. It is recommended that glassware be reserved only for use with the CAD, including mobile phase reservoirs, beakers, flasks, graduated cylinders, etc. Always rinse your glassware with a suitable solvent, followed by triple-rinsing with high purity, 18.2 MΩ·cm deionized water, followed by rinsing with the mobile phase solvent or weaker eluting mobile phase solvent when a solvent mixture is used as mobile phase. When not in active use, cover any open glassware to prevent the entry of dust.

Most laboratory glassware is cleaned in a laboratory dishwasher with strong detergents to remove contaminants. As the CAD is an excellent tool for the analysis of detergents and surfactants, it is recommended to either utilize a detergent-free cleaning agent, wash the CAD dedicated glassware manually, or take special care in rinsing the glassware after dishwashing and prior to use. After cleaning of glassware allow for air drying and refrain from the use of (paper) towels.

Although gravimetric and volumetric methods are nowadays considered state of the art, having largely replaced titrimetric eluent and buffer preparation recipes, some methods still prescribe the measuring and titrimetric adjusting of the pH. If using a pH meter during mobile phase preparation, keep in mind that pH electrodes are stored in concentrated solutions of potassium chloride. Residual drops on the electrode that are not removed by rinsing the electrode can introduce a measurable amount of this non-volatile salt to the mobile phase. In addition, as the electrode itself has a permeable glass membrane, the leaching of ions into the mobile phase is a source of contamination. Avoid immersing the pH electrode into the mobile phase and consider the use of small aliquots for pH measurements, which are discarded after the mobile phase pH adjustment is completed.

An item of special consideration is the selection of an appropriate vial. Vials consist of two parts – the body and the cap with septum – and each may be a source of contamination. Plastic vials can leach plasticizing agents, catalysts, and other compounds. Glass vials may leach

inorganic ions such as silicate, borate, and sodium. These contaminants can contribute to the void response and produce baseline artifacts and ghost peaks. Refer to section 3.5 How to determine the usability of vials.

2.4.2 Mobile phases and additives

A major factor affecting CAD performance is the concentration of non-volatile and semi-volatile impurities in the mobile phase. Higher levels of impurities lead to higher background currents, higher baseline noise, and more pronounced baseline drift.

In general, for mobile phase solvents and additives, the requirements are the inverse to those of the analytes. Solvents and additives need to be volatile at operating conditions. Among the most common solvents used with HPLC, water is the least volatile. CADs are designed to be compatible with 100% aqueous solvents at the detector's maximum specified flow rate. Therefore, since most organic solvents are more volatile than water, the vast majority of solvents commonly used with HPLC meet the requirement for volatility.

For additives, the situation is slightly more complex as commonly used buffer components (e.g., sodium phosphate), and ion pairing reagents (e.g., octanesulfonic acid) are inherently non-volatile and should not be used with the CAD. Fortunately for most methods, volatile additives such as formic acid, ammonium formate, or ammonium acetate and volatile ion pairing reagents including trifluoracetic acid (TFA), pentafluoropropionic acid and heptafluorobutyric acid are suitable alternatives.

In addition to the general requirement to use volatile solvents and additives, the level of semi-volatile and non-volatile impurities in these mobile phase components is an important consideration as further discussed below.

An example showing the relationship between the mobile phase quality and CAD performance is presented in Figure 4, and corresponding performance parameters are summarized in Table 1. As can be seen, the use of a poor mobile phase quality (prepared by using contaminated TFA as additive) results in high noise, large drift, baseline artifacts as well as mobile phase contaminant peaks eluted with the gradient, and a poor analyte response. For details refer to Technical Note 159: Effect of mobile phase quality on analytical performance of Corona Charged Aerosol Detectors.[6]

Table 1. Example for effects of mobile phase quality on CAD performance. In the application, TFA containing water and acetonitrile were used for a gradient-based assay of a non-volatile analyte, where two batches of TFA (degraded and fresh) were compared.

Metric	Poor mobile phase quality	Good mobile phase quality
Background current (pA)	20	2
Detector noise (fA)	600	36
Assay LOQ (S/N = 10) (ng o.c.)	1540	15
Assay LOD (S/N = 3) (ng o.c.)	465	5
Average (n = 3) SNR (710 ng o.c.)	4.6	350
Calibration curve R^2	0.9507	0.9999
Precision range (% RSD)	6.2–11	0.34–5.39

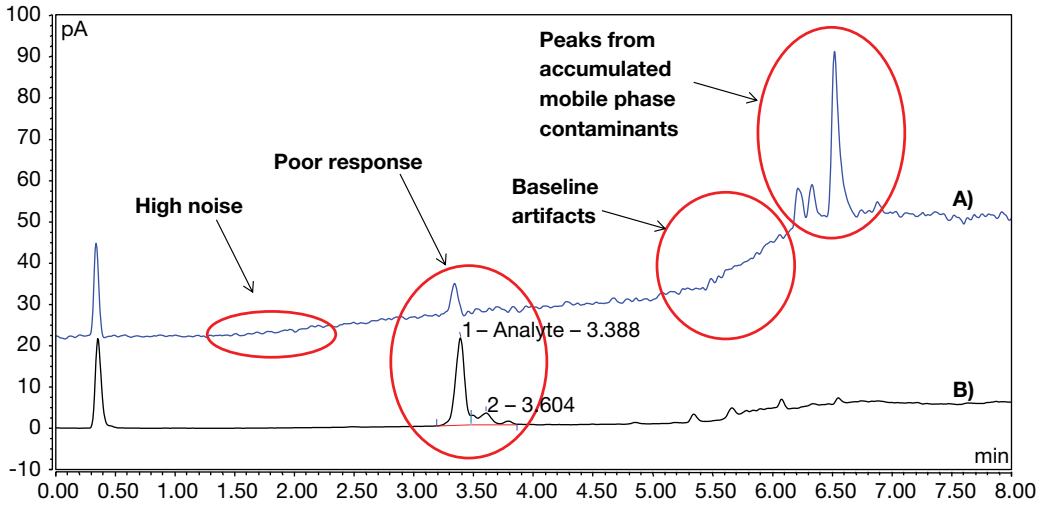


Figure 4. HPLC-CAD gradient analysis of a non-volatile analyte (2840 ng on column (o.c.)) A: blue trace using mobile phase with contaminated additive, B: black trace using good quality phase prepared with fresh additive). Indicators of poor mobile phase quality are shown in the figure.[6]

2.4.3 Organic solvents

All vendors provide labels on each solvent bottle that display various product specifications. Choose solvent grades that contain the lowest “residue after evaporation” specification. Be aware that not all vendors have the same “residue after evaporation” specification for a given grade of solvent and there are no universal classification rules for solvents.

Some grades of organic solvents contain additives, e.g., THF is often stabilized by addition of 100 to 300 ppm butylated hydroxytoluene. These solvents are best to avoid. Be aware that some grades that are considered highest purities are usually tailored for a specific purpose (e.g., electrochemical grade or spectrophotometric grade) and are optimized to contain the least possible amount of a certain class of impurities (e.g., redox active or chromophoric contaminants) but still may contain significant levels of impurities of other classes. As the requirements are highly similar between a CAD and an MS, it is recommended to preferentially use solvents that are designated as LC/MS grade or better, keeping in mind that there are most often no universally accepted definitions and specifications for quality grades, making the comparison between different manufacturers and brands difficult.

Quality of solvents can vary greatly between manufacturers but also between different lots from the same manufacturer, e.g., for HPLC-MS grade methanol. The residue after evaporation is often found in a range between “none detected” and 5 ppm. If possible, select bottles from batches with the lowest residue after evaporation. To illustrate this, Figure 5 shows the differences in CAD performance for different batches of methanol.

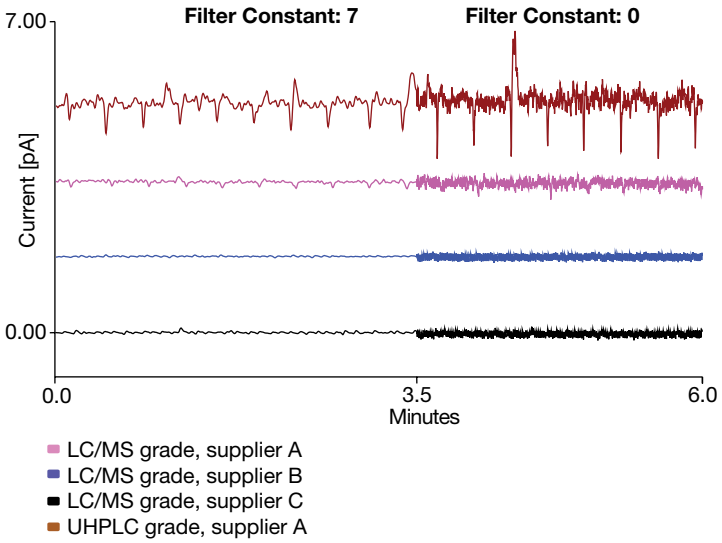


Figure 5. CAD baseline behavior for four different commercial sources of methanol. Black, blue, and pink traces – LC/MS grade; brown – UHPLC grade. Two filter constants are shown: 7 (0–3.5 min) and 0 (3.5–6.0 min). For details refer to Technical Note 140: Optimizing and monitoring solvent quality for UV-Vis absorption, fluorescence and charged aerosol detectors.[7]

2.4.4 Water

A very common cause for high background currents is a high level of impurities in the water used for mobile phase preparation. Whenever possible use Type 1 (ultrapure) water as defined by ASTM D1193 with key specifications of 18.2 MΩ·cm or greater resistivity at 25 °C and maxima of 50 ppb total organic carbon, 1 ppb sodium, 1 ppb chlorides, and 3 ppb total silica. This should be obtained from a point-of-use water source where best results are obtained when the feed water is purified by reverse osmosis. This combination provides a source of water which goes through multiple filtration treatments and effectively removes impurities. Ensure that the water system is regularly maintained and kept in good working order. When taking water from the water source it is recommended to discard the first 50–100 mL fraction. If the water source has been left idle for some time (e.g., when not in use overnight), do not use the initial first 500 to 1000 mL of water with the CAD.

If such a point-of-use water system is not available, a high-grade of bottled water with low levels of impurities is recommended, such as UHPLC-MS grade water, although use of bottled water will usually produce higher background currents and noise levels than fresh ultrapure water.

2.4.5 Additives

The mobile phase may include additives such as pH modifiers, buffers and ion pairing reagents. In method development for HPLC-CAD, the choice of mobile phase additives is an important topic. With a CAD it is recommended to simultaneously consider the effects of mobile phase additive type and concentration on both

the chromatographic separation and on detection. A key consideration when using a CAD is that additives that are normally considered to be volatile can form less volatile salts with other ionic species that coexist within a given aerosol droplet. The other ionic species may be analytes, other additives, impurities, or sample matrix components. For example, as previously described, chloride is expected to be too volatile to detect with a CAD but if ammonium is used as an additive, then a detectable non-volatile salt can be formed. Formation of a non-volatile salt can be beneficial, for example, if chloride is an analyte of interest but can be detrimental if chloride is an eluent impurity or a sample matrix component.

The influence of additives on response uniformity is detailed the Technical Note 72806: Charged aerosol detection - factors affecting uniform analyte response.[1] Usually, an increase in background current and noise is observed whenever an additive is utilized. This effect increases with additive concentration and with a decrease in additive volatility. It is therefore recommended to restrict the concentration of additives to the minimum required to achieve the desired separation. More importantly, low molecular weight additives are recommended (e.g., formic acid should be chosen over TFA or acetic acid) since any salt formed with impurities should be more volatile and therefore contribute less to the background. The effect of additive concentration on the observed noise is shown in Figure 6.

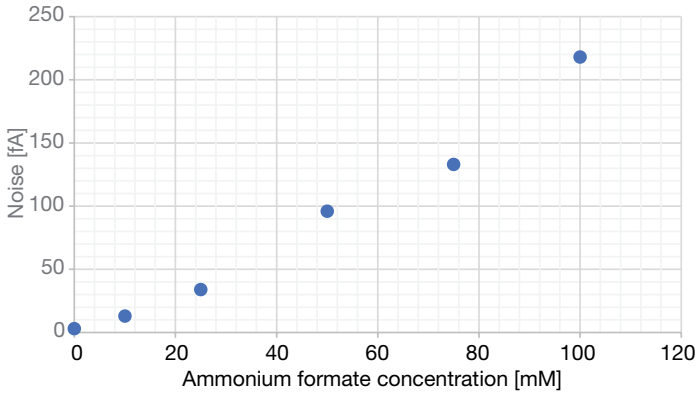


Figure 6. Observed noise at different concentrations of a volatile additive. The CAD was used at default settings with 1 mL/min isocratic flow of ammonium formate dissolved in 80/20 (v/v) water/methanol.

The influence of additive volatility is most significant when using ion pairing reagents such as TFA and higher molecular weight acids or triethylamine (TEA) and higher molecular weight bases since, by their nature, they tend to form non-volatile salts with impurities producing high background currents. It is recommended to avoid the use of TFA or longer chain (higher MW) acids together with ammonium or other basic additives. Likewise avoid using higher MW basic (e.g., butylamine, TEA) additives together with formic acid or other acidic additives. These additive combinations will, by themselves, form salts often leading to prohibitively high background currents and baseline noise. Ion pairing reagents can also form salts with ionic sample matrix components which, if present at sufficiently high enough levels, can lead to a large solvent front, ghost-peaks, or other baseline artifacts. In general, whenever additives are used, the optimization of the T_{Evap} is crucial in achieving the best performance. An example of the influence of T_{Evap} on the observed noise is presented in Figure 7.

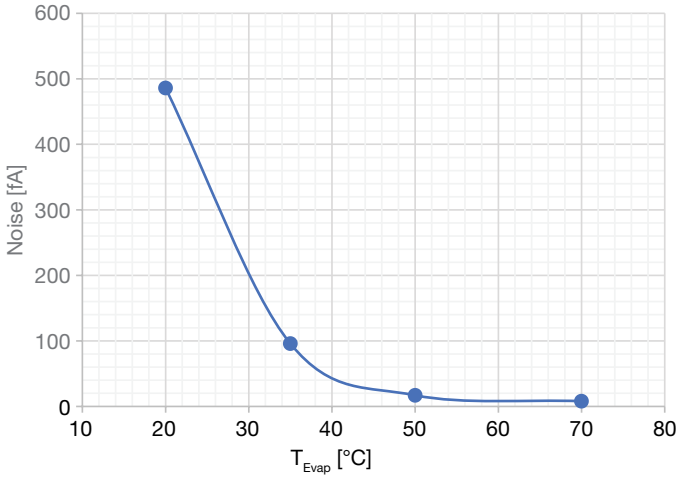


Figure 7. Observed noise for a 50 mM ammonium formate solution as a function of the set T_{Evap}. The CAD was used at default settings with 1 mL/min isocratic flow of ammonium formate dissolved in 80/20 (v/v) water/methanol.

Like solvents, any kind of additive should always be sourced as a high purity chemical (in general LC/MS grade is recommended). As a general guide any additive should only be used at the lowest level necessary for a method and evaluating the additive level should be part of method development.

For these and other reasons it is sometimes preferable to use a mixed mode column instead of ion pairing reagents. Many mixed-mode columns (e.g., reversed phase + ion exchange, or HILIC + ion exchange) are available today and changing the separation mode can help to avoid the issues of ion pairing agents discussed above.

Ammonium carbonate eluents produce high background current and noise. This can be mitigated by using a higher T_{Evap} (e.g., 50 °C). Interestingly, ammonium acetate eluent when used at a similar pH, initially shows low background current and noise, but these slowly increase over time. Such increases are likely due to the formation of less volatile carbonate salts produced when atmospheric carbon dioxide is absorbed by the eluent. If chemical interaction between the mobile phase and atmospheric components is observed, shelf lives will be short and careful monitoring of background current is mandated.

Ion exchange chromatography with sodium hydroxide eluents is typically used for separation of carbohydrates and similar compounds. As sodium hydroxide is non-volatile it must not be used with the CAD. Interestingly, ion exchange chromatography with a sodium hydroxide mobile phase can be compatible with the CAD if sodium ions are removed before the eluent enters the CAD. This can be achieved using post column on-line ion suppression. By using this approach, ion exchange chromatography with basic eluents can be used routinely with the CAD.[8]

2.4.6 Solvent aging

The age of the mobile phase can also affect CAD performance (Figure 8). Aging of solvents, i.e., change of solvent with time due to interactions with environment, containers, etc. is often found to contribute to the background current and noise of the CAD, whenever proper shelf lifetimes are not enforced.

The processes that lead to solvent aging differ depending on the solvent type. For water, the dominant processes are ion leaching in a shorter time scale and microbial growth

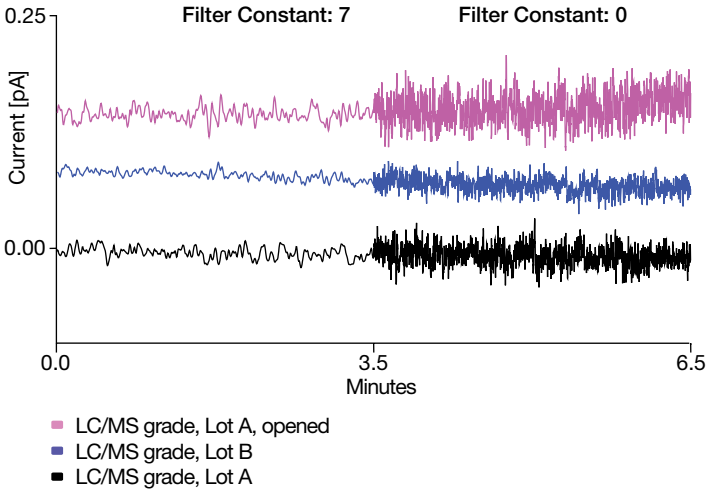


Figure 8. Effects of solvent storage on CAD baseline behavior. Black – fresh bottle of LC/MS grade acetonitrile (ACN) (lot A) used directly; pink – same bottle of ACN lot A but used following repetitive opening and closing of solvent bottle; blue – different lot.[7]

over longer periods. Microbial growth is more pronounced in aqueous buffers and is minimized by the presence of at least 5% organic modifier.

Organic solvents often react with atmospheric oxygen and aging after opening of a solvent bottle is observed for all organic solvents. It is therefore recommended to avoid the use of solvents that have been exposed to air for a prolonged time. Choose the size of reservoir bottles according to solvent use to ensure the shortest shelf time possible.

2.5 Columns

Current versions of the CAD are compatible with flow rates up to 2.0 mL/min so they can be used with all commonly available analytical column formats. While early CAD methods were developed using the classical 4.6 mm inner diameter columns, the use of smaller inner diameter columns (e.g., 2.1 mm inner diameter UHPLC capable columns) is nowadays preferred as this leads to better analytical performance (higher signal intensities, less noise from column bleed, see discussion below) as shown in Figure 9. Furthermore, UHPLC approaches are more compatible with the inverse gradient solution (see above).

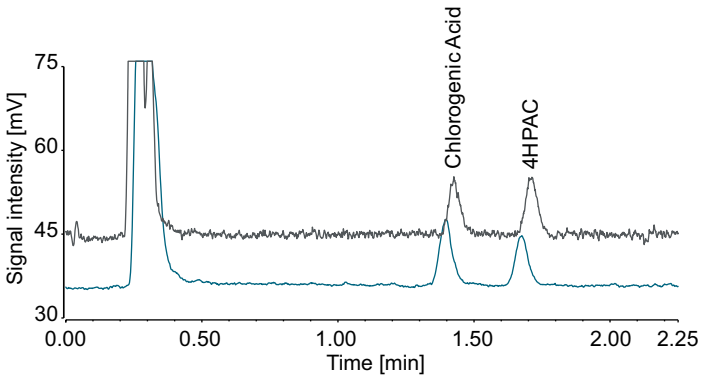


Figure 9. Comparison of observed noise for two columns of different inner diameter but identical column material (Acclaim RSLC C18, 2.2 µm, 3 × 50 mm in gray, and Acclaim RSLC C18, 2.2 µm, 2.1 × 50 mm in blue). Achieved signal-to-noise ratios are about threefold higher for both analytes when using the 2.2 µm, 2.1 × 50 mm column.

2.5.1 Column bleed

Column bleed is the introduction of semi-volatile or non-volatile impurities from the column itself, typically the result of stationary phase degradation (release of bonded phase material and the dissolution of the solid phase support material itself) or a memory-effect of columns previously used for other applications, especially when ion pairing agents or non-volatile buffers were used. Some columns show significant bleed throughout their operating pH range (e.g., silica-based amino and cyano columns) while others only show significant bleed when operated near the extremes of their pH or temperature range (e.g., silica-based C18 columns). Silica-based stationary phases (e.g., with amino, diol, or zwitterionic functional groups) when used with HILIC under neutral or slightly basic conditions, can exhibit significant bleed. If this is the case, select columns with a wide pH compatibility (e.g., polymeric, protected silica or a more pH-stable support).

High column temperatures may also be associated with an increase in column bleed. If this is the case, choose the lowest column temperature that still provides a positive impact on the chromatographic separation while minimizing column bleed.

Remember, although column bleed with its associated increased in noise and background currents may be observed, column performance is often acceptable, and columns may still show fairly stable retention times and peak shapes.

2.5.2 Conditioning protocols

When using a column for the first time it is recommended that it is washed overnight with a stronger eluent at a slightly increased operating temperature. Prior to use, change to the operating mobile phase and temperature. Allow time for the column to reach equilibrium before evaluating. If using a gradient, allow the column to experience several gradient cycles prior to use.

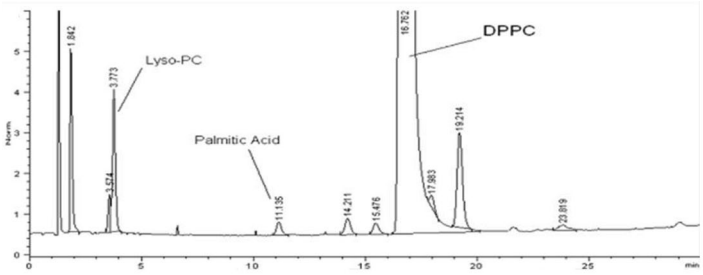
For cleaning procedures, manufacturers provide suitable protocols. These can help recover the column performance and reduce the noise levels as well as observed background current. Keep in mind that this approach is only feasible if a contamination from analysis of multiple samples is suspected. For most columns it is not economically feasible to undergo prolonged cleaning using high purity solvents to re-establish good performance of the CAD after a column has been exposed to non-volatile additives. Instead, only use dedicated columns with the CAD.

2.6 Standards

In addition to the noise and background current observed for a particular chromatographic method, the accuracy of results will also depend on the quality of calibration. The calibration, in turn, depends upon the quality of the standards being used.

For commercially available standards, purity level is often determined by a single analytical technique that may miss the contribution of some impurities. Check the label or refer to the compound's certificate of analysis to find out more about how purity was determined. For example, Figure 10 shows the measurement of a lipid standard reported by the manufacturer to be 99%+ when determined by TLC. However, when measured by HPLC-CAD the purity was found to be only 96.1%.

Expanded view of 10 µg DPPC



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.842	MM	0.1097	29.79032	4.52400	0.8747
2	3.574	MF	0.1207	6.78948	9.37327e-1	0.1993
3	3.773	FM	0.1507	31.68235	3.50353	0.9302
4	11.135	MM	0.2735	5.36398	3.26847e-1	0.1575
5	14.211	MM	0.2920	7.14583	4.07800e-1	0.2098
6	15.476	MM	0.3081	5.26313	2.84673e-1	0.1545
7	16.762	MM R	0.3767	3272.21021	144.79330	96.0736
8	17.983	MM T	0.2241	3.94442	2.93356e-1	0.1158
9	19.214	MM T	0.2800	39.18480	2.33210	1.1505
10	23.819	MM	0.5384	4.56571	1.41342e-1	0.1341

Purity of commercially available DPPC standard reported to be 99+% by TLC, but found to be 96.1% by CAD.

Figure 10. Determination of standard purity depends upon the analytical technique used. Comparison of HPLC-CAD vs. TLC methods for the determination of the purity of a commercially available dipalmitoylphosphatidylcholine (DPPC) standard.

Some standards may be hygroscopic (absorb moisture from the atmosphere) or deliquescent (absorb moisture from the atmosphere and dissolve in it) – both problematic when making standards for calibration studies. Some compounds may be unstable when exposed to the atmosphere or degrade when dissolved in solvent. Check information provided by the manufacturer. To overcome these issues, purchase small quantities of standards (preferably in single use sealed vials) or store standards over desiccant. Make sure the desiccant is active and replace it if necessary. Record in a logbook when the standard was purchased, when first opened and whenever it was used. Set appropriate expiry dates and replace if necessary. It can also be beneficial to use pre-weighed sealed ampules for standard preparation.

2.6.1 Estimation of quantity in the absence of individual standards

Chromatographic methods rely on the availability of individual standards for quantitation, but reference standards are not always available (for example, during drug discovery). Furthermore, the purity of the drug candidate may be unknown. UV absorbance and MS detectors are commonly used to quantify analytes, but the response of these detectors depends upon the compound's chromophoric properties or ability to form gas phase ions, respectively, making a quantitation difficult for some compounds.

As the CAD shows uniform response for all non-volatile analytes it is ideal if quantitation is needed and no reference standards are available. With a single calibrant the quantification of multiple analytes is therefore possible, even in the absence of individual standards. Remember that as the CAD response is dependent upon mobile phase composition, an inverse gradient is required when using gradient elution.

3 Part B. Best practices

In this section we present many tips for the routine use of the CAD. Please be aware that the operating manuals remain the primary source of user information – see here.

3.1 How to start up and equilibrate the CAD

In addition to the general good practices and considerations when utilizing HPLC, please observe the following guidelines when preparing the CAD for operation:

- Temperature fluctuations can affect the performance of the detector. Avoid locations with significant changes in temperature and strong air drafts. For example, do not place the detector in the direct sunlight, near heating or cooling sources, or under an air duct.
- Verify that the correct nebulizer gas pressure setting, as stated in the nebulizer certificate, is set on the device or in the software depending on the model.
- **Always turn on nitrogen gas flow prior to turning on the liquid flow.** Wait at least 5 minutes after turning on the gas flow before turning on the liquid flow. Failure to do so can flood the detector.
- Ensure that an upper flow rate limit is set in the control software, so as to not exceed the flow rate rating of the CAD.
- Like lamp temperature equilibration for VWD or DAD, the CAD should be allowed to equilibrate prior to starting an analysis: wait until baseline stability is obtained. Make sure to equilibrate the CAD using the final analysis conditions (T_{Evap}, mobile phase composition, flow rate, etc.). The baseline and noise levels should be stable, this can be verified, e.g., using the built-in function in Chromeleon CDS software to check for noise and drift.

3.2 How to shut down a HPLC-CAD system

When not in use, it is often desired to shut down the CAD to conserve gas, mobile phase(s), etc. For short stand-by periods, e.g., overnight, it is recommended to maintain the gas flow to the CAD but reduce the mobile phase flow rate to 50 µL/min, until normal operation is resumed. Remember if stopping mobile phase flow to the CAD make sure that gas flow is maintained. Never switch off gas flow while mobile phase is flowing. Failure to do so may flood the CAD and cause damage.

For a prolonged shut-down period, the CAD should be prepared as follows. First, with the column removed from the flow path, clean the system and detector with a mixture of high purity water and methanol 50/50 (v/v) for at least 1 hour. If either a high background current, pronounced drift, or a high noise level is observed, this flushing period should be extended until good working conditions are restored. Periods of increased T_{Evap} (e.g., 20 minutes at 35 °C, 20 minutes at 70 °C, 20 minutes back at 35 °C) can help to achieve good operating conditions faster. If the detector is intended to be stored for a prolonged time or as a preparation for transportation, follow this step by flushing the detector with pure isopropyl alcohol for 10 minutes.

Second, after flushing, turn off the pump to stop the flow of mobile phase to the CAD. Leave the gas flow on for at least 5 minutes until the CAD is completely dry.

Following this procedure is not only necessary to minimize safety risks by removing hazardous materials, but it also ensures that no residues left when mobile phase solvents evaporate are present anywhere in the CAD. Otherwise, remaining static liquids, especially when containing acidic modifiers, may lead to corrosion of components inside the CAD. Remember that for all shut down procedures it is necessary to keep gas flow on after stopping liquid flow.

3.3 How to check mobile phase quality

In order to adequately evaluate the quality of a new batch of mobile phase, especially when using a new type or lot of solvent or additive, it is important to establish a frame of reference as well as continuously monitor the performance of each application.

One approach to evaluating mobile phase quality is to first verify the detector performance using qualification conditions. For example, measure the noise with a methanol/water (20/80, v/v) mobile phase, a flow rate of 1 mL/min, and the following detector settings: T_{Evap} 35 °C, data collection rate 10 Hz, and a filter constant of 5. Replace the column with a restriction capillary (or only a small cartridge). Under these conditions noise should be less than 40 fA.

Once the baseline noise is known, other mobile phases, solvent lots, brands, additives, etc. can be quickly screened. This can be automated by installing a large loop in a suitable valve in the system (e.g., on a 6 port-2 position valve in the Vanquish Thermostatted Column Compartment), which must be located after the autosampler, as shown in Figure 11.

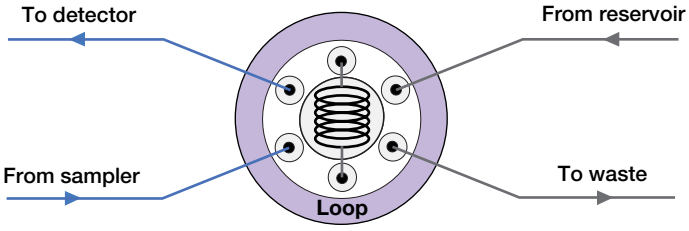


Figure 11. Schematic of setup to test mobile phases

The loop is flushed and filled with the mobile phase that is being tested (e.g., by using the gravitational pull on the solvent connected with a solvent line to the valve, or with a large volume syringe) and a simple method including valve switching then allows direct measurement of the background current and noise of the new mobile phase being tested compared to the approved reference mobile phase (Figure 12). The advantage of this setup is that it is direct and rapid and does not require extensive purging and flushing of the system.

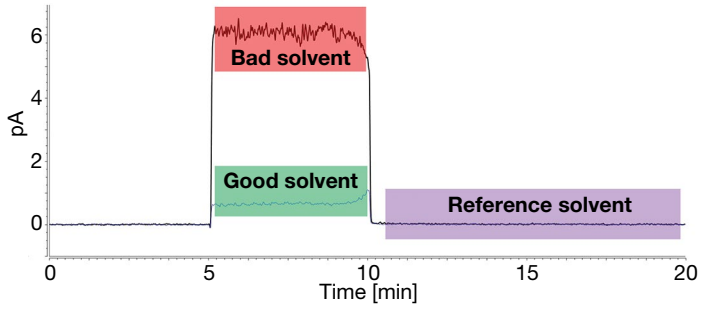


Figure 12. Testing of suitability for different solvents. Reference Solvent is a mixture of 80/20 freshly prepared ultrapure water from a point-of-use water source with Fisher Chemical™ Optima™ LC-MS grade methanol. Green box (good solvent) is 80/20 Fisher Chemical bottled UHPLC-MS grade water with UHPLC-MS grade methanol. Red box (bad solvent) is a mixture 80/20 of ultrapure water with Optima LC-MS grade methanol that was left to age for 2 weeks.

The conditions can easily be used to screen the quality of pure solvents. Given that the observed background currents not only depend on the mobile phase solvents, additives (see Figure 6) and composition, but also on the detector settings (e.g., the T_{Evap} (Figure 7), data collection rate, filter constant), the settings should be adapted to match the intended chromatographic method. Although this approach may be convenient and time saving when developing a mobile phase for the first time (e.g., selecting between vendors, evaluating differences in solvent grades, and determining lot-to-lot variability etc), it may be overkill when testing a routinely made mobile phase.

3.4 How to establish best practices for preparing mobile phases

As outlined previously, when preparing mobile phases, always use dedicated, triple rinsed glassware. Mobile phase should be prepared freshly prior to use. Only use fresh water for the preparation of mobile phases. For aqueous mobile phases, it is recommended to prepare the mobile phase daily, organic based mobile phases should be prepared at least on a weekly basis. For all commercial solvents, record lot number and solvent quality. Document the residue after evaporation for a given lot of solvent. Using a permanent marker, log date received and opened to avoid using contaminated / old solvents inadvertently. If a different grade, supplier, lot etc. of the solvent is used, consider testing the solvent against a solvent of known quality as outlined above. Do not store mobile phases for later use as impurities and contaminants can increase over time.

For best results choose single use glass ampules for organic acids such as TFA and formic acid. Use fresh and do not store once opened. Some additives (e.g., TEA) once exposed to the atmosphere form non-volatile impurities that can contribute to noise. Whenever possible, purchase small quantities and minimize the number of times the bottle is opened. In some cases, e.g., when high purity additives are not commercially available, as is the case for some ion pairing agents, the use of trap columns between the pump and autosampler can help to reduce the impact on an assay's performance.

Do not filter the mobile phase as the filtration process can lead to contamination with particulates/fibers from the filter material. Degassing eluents is essential to prevent problems caused by dissolved gas. This is typically achieved using online vacuum degassers (usually an integrated part of modern HPLC and UHPLC systems). If this is not possible, then degassing of mobile phase by sonication is recommended. Degassing by vacuum filtration through a membrane should be avoided, as it might lead to contamination as mentioned above.

3.5 How to determine the usability of vials

Before selecting an autosampler vial it is important to check whether it negatively impacts analytical performance. For example, fill vials with mobile phase and each of the solutions used for sample and standard preparation. Cap, vortex, and leave for about 72 hours. Vortex each day to make sure the cap is exposed to the solution in the vial. Analyze the contents of each vial and see if:

- The solvent front changes (does it impact early eluting peaks?).
- Impurity peaks appear in the chromatogram (do they affect analyte peaks of interest?).
- The baseline behaves as expected or are there large perturbations in the chromatogram? (These can result from the elution of strongly retained compounds from previous injections).

If there are no issues, then the vial and cap are safe to use. If there are issues, other caps/vials will need to be evaluated. A comparison of three types of vial-cap combinations for an assay using a mixed mode column is shown in Figure 13. Note that with the conditions of the assay, retention of small ionic components is observed. Therefore, one of the vial-cap combinations was rejected, but even so, it may be suitable for use with a different chromatographic method.

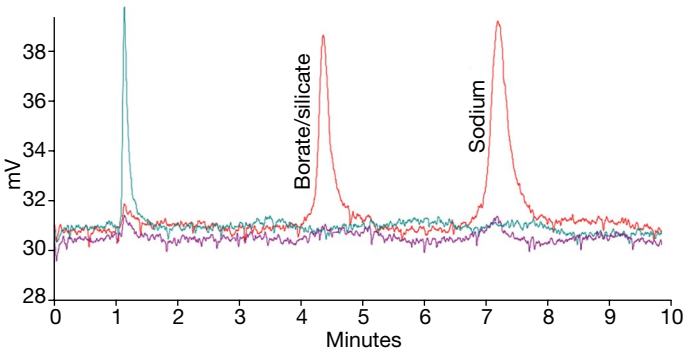


Figure 13. Comparison of three different vials. A significant amount of ionic leachables can be seen in a non-passivated vial (red line). Another vial type shows a high amount of unidentified leachable (blue line) eluting in the void volume. A third vial did not show any significant amount of leachables and was therefore accepted for use with this method (purple line).

3.6 How to utilize FIA during method development

FIA is an invaluable tool for troubleshooting used at the beginning of the method development process. The use of FIA allows quick answers to two questions:

1. Is my analyte of interest detectable by the CAD or is it too volatile?
2. Is my analyte of interest behaving as a semi-volatile or as a non-volatile?

Using FIA is simple. A solution of the analyte of interest prepared in a suitable solvent is injected into the stream of mobile phase entering the detector. While a column is not used, a backpressure capillary replaces the column to ensure that the (U)HPLC pump achieves the required minimum pressure for stable flow rate. When possible, avoid the use of mobile phase modifiers at this point. Typically, it is recommended to dissolve the analyte in a mixture of water and methanol or water and acetonitrile in ranges of 10 to 50% organic solvent.

To verify the absence of matrix effects, perform a series of injections with concentrations varying in the targeted concentration range in addition to mobile phase and blank runs. Use default detector settings initially (T_{Evap} 35 °C, 10 Hz, 5 s). The results will show whether the CAD is a suitable detector for this analyte.

To investigate whether a particular analyte behaves as a non-volatile or as a semi-volatile, several approaches can be used. Experienced users may be able to predict differences in volatility based solely upon the shape of the response curve at low concentration levels.[8] A more foolproof approach is to compare the response area to that of a known volatile under identical conditions, as all non-volatiles exhibit very uniform response (see Figure 1). The best approach, however, is to repeat the FIA experiments at different T_{Evap} settings (e.g., 40 °C on the Corona Veo RS or Thermo Scientific™ Vanquish™ Horizon UHPLC system CAD, or 50 °C on the Thermo Scientific™ Corona™ Veo or Thermo Scientific™ Vanquish™ Charged Aerosol Detector F. If the peak area stays fairly constant (e.g., Area (40 °C)/Area (35 °C) ≥ 0.9), a non-volatile's behavior at the lower T_{Evap} can be assumed. Note that analytes which behave as non-volatiles at low T_{Evaps} may still show semi-volatile behavior at higher T_{Evaps}. This must be considered during method development.

3.7 How to perform cleaning of a HPLC-CAD system

If the CAD consistently shows high noise and it has been established that the noise is not introduced by the (U)HPLC-system, solvents, etc., it is likely that a contamination of the nebulizer, spray chamber or evaporation tube may be the root cause. A flushing procedure can help to remove these contaminations and restore the CAD performance. First, clean the system by flushing it (without a column) with a suitable cleaning solvent mixture, e.g., the Thermo Scientific™ ChromaCare™ LC-MS Instrument Flush Solution: a quaternary mixture of LC/MS grade acetonitrile, methanol, water, and 2-propanol, or a 50/50 (v/v) mixture of water/methanol. The flushing should be performed while monitoring the background current. In most cases, the background current will decrease over time and after several hours a normal background current is achieved. Periods of increased T_{Evap} (e.g., 20 minutes at 35 °C, 20 minutes at 70 °C, 20 minutes back at 35 °C) can help to re-establish good operating conditions faster. If after 24 hours of flushing the background current does not show a significant

improvement, a full preventive maintenance performed by a service technician, which includes a cleaning of the nebulizer, spray chamber, and evaporation tube, is recommended.

3.8 How to calibrate when using the CAD

To obtain accurate quantitation with any detection technique, it is important to choose an appropriate calibration model by performing a robust evaluation for quality of fit. For greater detail, see Technical Note 73299: Charged aerosol detection – use of the power function and robust calibration practices to achieve the best quantitative results. Briefly:

- Limit calibration to as small a range as possible above and below the expected sample concentration.
- Use the simplest curve fitting model that adequately describes the response-amount relationship over the required range of interest. A linear curve fit can often be used when quantitating over a range of 2 orders of magnitude. For quantitation over wider ranges, quadratic (i.e., 2nd order polynomial), log-log and point-to-point options are commonly used.
- Evaluate quality of fit by using at least 5 levels and 3 replicates at each level over the entire range with special consideration to the upper and lower limits.
- Do not use aggregate measures (e.g., coefficient of determination (R^2), residual sum of squares (RSS)) as the only metrics for assessing quality of fit, since deviations, especially near lower analyte amounts, may be under-represented.

A curve fit with an R^2 of 0.9990 may still be poor, with the largest error typically near the low end. Reliance only on R^2 is especially problematic when using a log-log curve fitting model. For these reasons, it is highly recommended to use residuals plots as additional means to assess the quality of curve fit.

Most detector response data can be described as heteroscedastic, where peak area variability is greater for higher analyte amounts. This larger variance may exert too much influence on a least-squares regression line. For this reason, it is often useful to use weighted regression (e.g., 1/amount, 1/amount^2) to counteract the influence of higher amounts on the curve fit. This often provides a better fit to the lower amounts.

3.9 How to set the Power Function Value (PFV)

The PFV is a user-defined setting that allows optimization of the inherent (analog and digital) signal output. The sole purpose of the power function is to optimize the range over which the CAD response is sufficiently linear for a given method and its range of quantitation. Since non-linear response also affects peak shape and signal-to-noise ratio, an optimal PFV also provides more accurate and simplified calculation of measures of chromatographic performance (e.g., resolution) and limits of detection.

There are two principle guidelines for choosing a meaningful PFV setting depending on the analyte properties:

1. The practical range of useful PFV settings for non-volatiles should be between 1.0 and 1.6.
2. Use of a PFV other than 1.0 is not recommended for analytes behaving as semi-volatiles.

The general approach to determine the optimal PFV setting is therefore to assess quality of fit for PFV settings between 1.0 and 1.6. The optimal PFV can be determined experimentally or by using the “Power Law” feature within the Chromeleon CDS software. For more details see Technical Note 73299: Charged aerosol detection – use of the power function and robust calibration practices to achieve the best quantitative results.[9]

Remember:

- Any use of a PFV < 1.0 will likely result in greater deviation from linear response and is not recommended.
- Use of a PFV > 1.7 will likely result in a sigmoidal curve shape and is therefore not recommended.
- The choice of a PFV should not be based on improving (apparent) SNR or peak shape.

PFV should only be chosen to linearize response rather than to artificially sharpen peaks or to exaggerate the SNR values for high level standards. Keep in mind that nearly all method performance parameters (e.g., chromatographic efficiency, resolution, signal-to-noise, limit of detection, limit of quantitation, etc.) are defined and valid only for sufficiently linear response. Applying measures which are defined for a linear behavior to a non-linear calibration curve can lead to misleading interpretations.

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3.10 How to transfer methods from older instruments

The steps needed to transfer a method from earlier model Corona detectors to Corona Veo and Vanquish Charged Aerosol Detectors have been covered in detail in Technical Note 71290: Guidelines for method transfer and optimization—from earlier model Corona detectors to Corona Veo and Vanquish charged aerosol detectors.[10]

Briefly:
It is highly recommended that the respective default settings of Corona Veo and Vanquish Charged Aerosol Detectors are used as a starting point for all method development.

- T_{Evap} = 35 °C
- PFV = 1.0
- Filter Time Constant = 5.0 s

Remember when comparing chromatographic data between a Corona Veo or Vanquish CAD and an earlier model Corona detector, using the default conditions, it is fairly common to see a somewhat higher baseline level, noise and drift with Corona Veo and Vanquish CAD. This is typically due to a non-linear drop-off in sensitivity of the earlier Corona models at the extreme low end of the dynamic range. This drop off in sensitivity can mislead the user to think that the achievable lower limits of detection or quantitation with the Corona Veo or Vanquish detectors are poorer than that of earlier models. However, this is more likely due to the better sensitivity (relative absence of signal drop-off) of Corona Veo and Vanquish CAD to very low levels of non-volatile residue.

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