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Pharma and biopharma

Why modernize universal LC detection?

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Keywords

Vanquish Charged Aerosol Detector P Series, temperature coupling mode, CAD vs. ELSD, biopharmaceutical formulation, drug formulation, impurity analysis, active pharmaceutical ingredient (API), liposome lipids, polysorbate (PS), lipid nanoparticles (LNPs)

Executive summary

For the pharmaceutical and biopharmaceutical industries, selecting the right detection technology is critical for identifying low-level impurities, accurately quantifying formulation components, and maintaining robust analytical methods throughout the method lifecycle. This white paper compares two widely used nebulizer-based liquid chromatography detectors: the charged aerosol detector (CAD) and the evaporative light scattering detector (ELSD).

Application examples discussed in this work demonstrate the improved performance of the CAD over the ELSD for liposome lipid analysis, lipid nanoparticle (LNP) composition analysis, polysorbate (PS) profiling, and impurity analysis across diverse pharmaceutical workflows. Overall, the CAD provides a compelling combination of high sensitivity, near-universal analyte response, and operational simplicity, making it suitable for a broad range of analytical applications. By comparison, the ELSD exhibits lower sensitivity, greater variability in analyte response, and reduced method robustness and reproducibility.

By delivering more reliable detection and quantitation, the CAD enables analysts to identify low-level impurities, degradants, and formulation changes that might otherwise go undetected, supporting confident decision-making throughout analytical development, process optimization, and quality control.

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Introduction

As pharmaceutical and biopharmaceutical workflows become increasingly complex, analytical laboratories require detection technologies that deliver flexibility, sensitivity, and reliability across a broad range of applications. Detector selection plays a critical role in ensuring accurate, high-quality data, robust analytical methods, regulatory compliance, and efficient laboratory operations. As a result, choosing the appropriate detector is a key consideration for supporting diverse analytical workflows and meeting the evolving demands of modern laboratories.

The most common detector used with high-performance liquid chromatography (HPLC) is the UV/Vis absorbance detector because of its excellent sensitivity, broad linear dynamic range, and compatibility with gradient elution methods. However, UV/Vis detection is inherently selective, as it relies on the presence of a chromophore within the analyte molecule. Consequently, compounds that lack suitable chromophores cannot be detected directly, limiting the applicability of this technique for certain pharmaceutical and biopharmaceutical analytes.

For compounds that lack chromophores, more universal detection techniques are used, including the CAD, the ELSD, mass spectrometry (MS), and the refractive index (RI) detector. RI detection is simple and widely applicable. However, its low sensitivity and incompatibility with gradient elution restrict its use to isocratic separations. MS can provide high sensitivity and specificity, but it may be complex to operate, requires analytes to form gas-phase ions, and often needs isotope-labeled standards for accurate quantitation. ELSDs are among the most widely used universal detectors for liquid chromatography, but they present several well-recognized limitations.

ELSDs typically exhibit a complex and sigmoidal response curve, lower sensitivity, limited linear and dynamic ranges, and analyte-dependent response variability. In addition, method development requires extensive optimization of multiple operating parameters, while routine maintenance further reduces instrument uptime. The CAD overcomes these limitations by delivering higher sensitivity, improved calibration linearity, broader dynamic range, more consistent analyte response, simplified method development requiring optimization of fewer parameters, and reduced maintenance, resulting in more robust and productive workflows. The CAD is the future of universal detection, supporting modernized workflows, greater efficiency, increased confidence in results, and a detector that is ready for tomorrow's challenges. To understand these benefits, the following sections examine the underlying CAD technology innovation and the performance across a range of applications compared to ELSD technology.

How detector choice influences analytical and operational performance

Both the CAD and the ELSD rely on comparable processes—nebulization, aerosol conditioning, and drying—to generate particles. As a result, they have similar detection ranges (covering non-volatile and some semi-volatile compounds), require similar eluents (volatile solvents and additives), and show comparable dependencies on solvent properties (with analyte response influenced by gradient conditions). Figure 1 shows schematics for both the ELSD and the CAD.

The key distinction between the CAD and the ELSD lies in how analyte particles are detected after nebulization and evaporation. In both techniques, detector performance is influenced by aerosol particle size, which affects the peak shape, response curve, detection limits, and precision. Particle composition also plays a critical role, influencing response uniformity and the extent to which the detector exhibits a truly universal response.

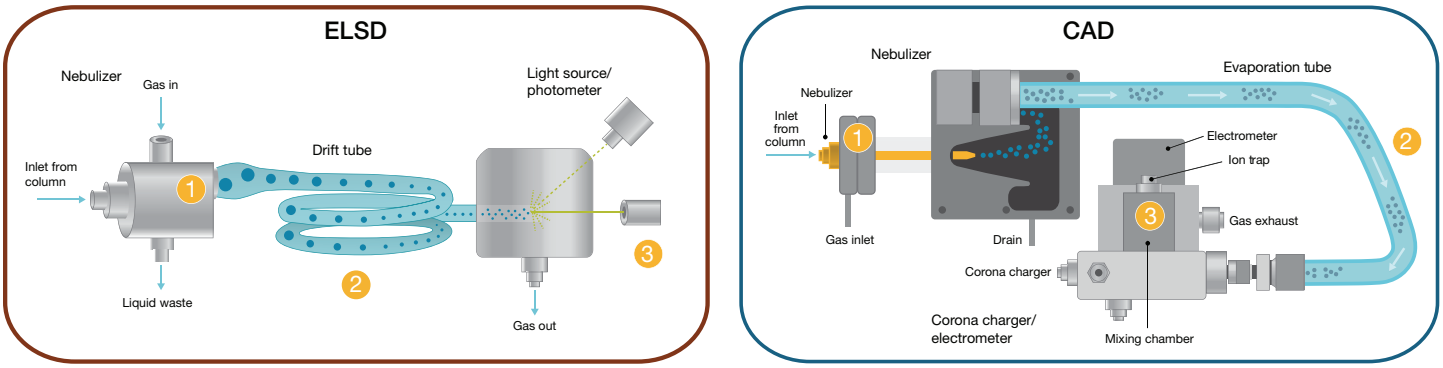


Figure 1. Schematic of the ELSD and the CAD: (1) nebulization, (2) droplet drying, and (3) particle detection. *This figure was generated using AI technology.*

The measurement principle of the CAD is simple and direct. Aerosol particles acquire an electrical charge, and the total charge is measured by an electrometer. Because the measured charge is directly proportional to analyte mass, the CAD provides a more consistent and predictable response across a broad range of compounds. In contrast, the ELSD response is governed by multiple light-scattering mechanisms that are highly dependent on both particle size and composition, resulting in a more complex and variable response.

Consequently, the ELSD generally exhibits greater response variability and more challenging calibration for quantification than the CAD[1] (Table 1). Additional information on detector response characteristics and their impact on analytical performance is provided in Appendix 1. These performance differences are supported by a recent review by Acworth and Gamache (2026),[2] which evaluated 28 peer-reviewed studies directly comparing the CAD and ELSD. Across the published studies, the CAD consistently demonstrated superior analytical performance, including higher sensitivity, more uniform analyte response, a broader linear dynamic range, improved precision, accuracy, reproducibility, and repeatability.

Both the CAD and the ELSD are widely used throughout the pharmaceutical and biopharmaceutical industries to analyze non-volatile and some semi-volatile compounds that lack suitable chromophores for UV detection. Their universal response makes them valuable for a broad range of applications, including the analysis of excipients, lipids, surfactants, carbohydrates, polymers, impurities, degradation products, and formulation components. As shown in Table 2, both detectors have been applied across diverse analytical workflows. Although they often serve similar analytical purposes, the choice between the CAD and the ELSD depends on the performance requirements of the method and ease of implementation.

The latest generation of CAD technology combines advances in detection performance, method development, workflow flexibility, and maintenance to address the key limitations associated with the ELSD.

Table 1. Application requirements and corresponding detector characteristics for the CAD and ELSD.

Key application requirement	Detector characteristics	CAD	ELSD
Near-universal detection	Analyte properties	Nonvolatile and many semi-volatiles	Nonvolatile and many semi-volatiles
Simple calibration strategy	Response curve	Curvilinear	Sigmoidal
Quantitation without surrogate standard	Response uniformity	Non-volatiles give similar response	Non-volatiles can give different responses due to particle's light absorption and refractive index
Quantify major and trace components in one run	Dynamic range (orders of magnitude)	4	2–3
Protocol/SOP requires linear calibration	Linear range (orders of magnitude)	1.5–2	≤1
Detect impurities	Limit of detection (LOD)	High pg – low ng	Low to mid ng
Application flexibility	Gradient compatibility	Yes	Yes

Table 2. Typical application examples in the pharmaceutical and biopharmaceutical industries applying ELSD or CAD.

Application area	Workflow	Typical analysis	Advantage of CAD over ELSD
Pharmaceutical	Impurity and degradation product analysis	Determination of a wide variety of analytes lacking a chromophore	Higher sensitivity, more uniform response
	Excipient quantification	Analysis of polymers, sugars, surfactants, and other formulation ingredients	Wider dynamic and linear range
	Drug formulation and development	Characterization of active ingredients and excipients during formulation optimization	Simplified method development
	Quality control	Measurement of release and stability testing of drug products	Greater robustness and less maintenance effort
	Cleaning validation	Measurement of non-volatile residue compounds from manufacturing processes	Higher sensitivity and broad dynamic range
Biopharmaceutical	Glycan analysis	Determination of N- and O-linked glycans	Higher sensitivity
	Lipid analysis	Measurement of LNPs, liposomal formulations, and other advanced drug delivery systems	Broad dynamic range
	Product characterization	Assessment of critical quality attributes (e.g., purity and stability) for biologics	Higher sensitivity
	Detection of residuals	Verification of removal of upstream additives/reagents (e.g., simethicone, Triton™ X)	Higher sensitivity
	Excipient quantification	Quantifying surfactants (e.g., PS) and other formulation components used in monoclonal antibodies, vaccines, and biologics	Simpler calibration, broader dynamic range and higher sensitivity

Modernizing universal detection workflows with CAD

First introduced commercially in the early 1980s, the ELSD is a mature and well-established detection technology. The CAD, while also a well-established technology, is a more recent innovation that has been commercially available for approximately two decades. Since its introduction, it has undergone continuous performance enhancements with a strong focus on ease of use and confidence in analytical results. The latest generation of Thermo Scientific™ Charged Aerosol Detectors—the Thermo Scientific™ Vanquish™ Charged Aerosol Detector P Series—is designed to address the key challenges associated with traditional ELSD technology. The Vanquish CAD P Series can help laboratories improve productivity while reducing the need for repeat sample analyses through the following advances in method development.

1. **Ease of method development.** The CAD simplifies method development by requiring far less optimization than the ELSD (Table 3). First, the CAD uses a single certified nebulizer across a wide flow rate range (0.01–2.0 mL/min), eliminating the need to switch nebulizers. It also automatically applies the optimal nebulizer gas flow based on the nebulizer's certificate of testing. In contrast, the ELSD typically requires different nebulizers depending on the flow rate and manual optimization of gas flow to achieve the best balance of sensitivity, baseline noise, and prevent spiking. Second, the CAD operates at a fixed ambient nebulizer temperature, eliminating the need for temperature optimization. Only the evaporation temperature (EvapT) is set. In contrast, the ELSD requires optimization of both the nebulizer and drift tube temperatures. Incorrect settings can increase baseline noise, reduce sensitivity, distort peak shape, or even result in analyte loss. Thus, the ELSD method development is more complex and time-consuming than with the CAD.

Table 3. Detector parameters that need to be evaluated during method development.

Component	Parameter	ELSD	CAD
Nebulizer+	Temperature	Manually adjusted by user	Fixed at ambient
	Gas flow (pressure)	Manually adjusted by user Requires manual replacement at low flow rates+	Factory certified. No adjustment is needed.
Drift/evaporation tube	Temperature	Manually adjusted by user	Manually adjusted by user
Signal output	Gain	Manually adjusted by user	NA
	Collection rate	Manually adjusted by user	Manually adjusted by user*
	Filter constant	Manually adjusted by user	Manually adjusted by user*
	Power value (PV)	NA	Selected by user

+Some ELSDs require switching between two nebulizers depending on the analytical flow rate.
*Method wizards of the controlling software can select best values based on expected peak width (Figure 2).

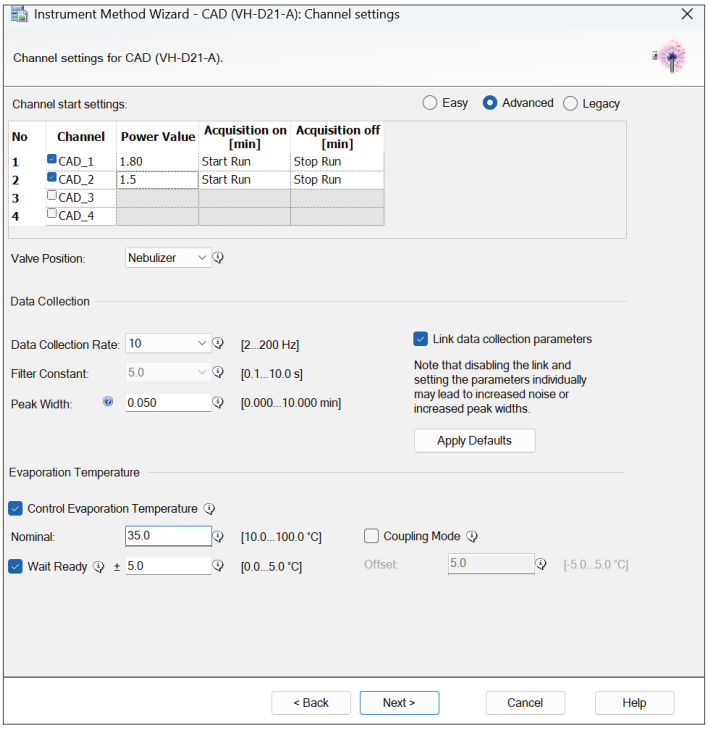


Figure 2. The Instrument Method Wizard for the Vanquish CAD P Series helps the user select the optimum values per default. In this example, the data collection rate and filter constant depend on the peak width.

2. **Greater sensitivity.** The temperature coupling mode extends the measurable range of semi-volatile analytes.[3]

3. **Enhanced calibration linearity for more accurate quantitation.** The power value (PV) function improves quantitative data analysis by linearizing the CAD response over a broader concentration range, enabling more accurate peak area comparisons and reducing post-processing effort.[4] The Vanquish CAD P Series can simultaneously acquire data using up to four different PVs from a single injection (Figure 2), significantly reducing method development time, sample consumption, and overall analytical cost.

4. **Flexibility.** The integrated three-way diverter valve lets users easily remove the detector from the flow path without replumbing the system. It can also divert unwanted matrix components to waste, reduce interferences, and improve the quantitation of early-eluting analytes (Figure 3).[5] In addition, the valve provides the flexibility to seamlessly direct the flow between the CAD and an alternative detector, such as an MS.[6]

5. **Minimal maintenance.** Routine detector maintenance is required to ensure optimal performance. As summarized in Table 4, the ELSD requires far more frequent and extensive maintenance than the CAD.

Together, these advances in method development, sensitivity, quantitative performance, workflow flexibility, and maintenance demonstrate how the modern CAD overcomes key ELSD limitations. The following case studies show how these benefits translate into practical analytical workflows.

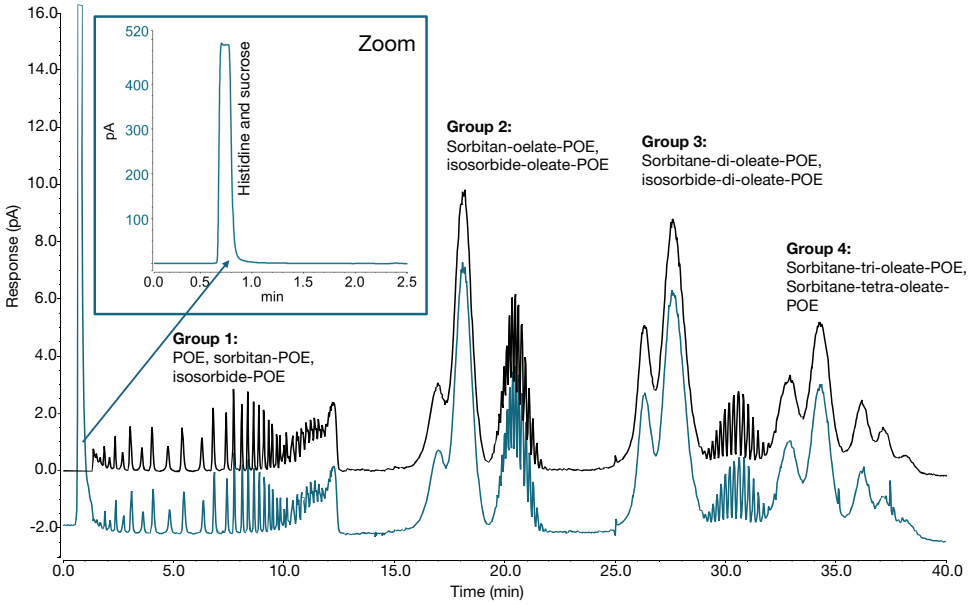


Figure 3. Overlaid chromatograms of a model formulation sample (PS 80 + histidine + sucrose) show the simplification of automated integration by using the integrated diverter valve. Black trace: diverter valve to waste (from 0 to 1.3 min) allows automated integration of group 1; blue trace: diverter valve to nebulizer (no switching).

Table 4. Comparison of CAD and ELSD maintenance requirements.

Component or maintenance consideration	CAD	ELSD
Evaporation / drift tube	Minimal maintenance is required	More critical: frequent cleaning is required
Charging unit (corona needle)	No maintenance is required	Not present
Electrometer	No maintenance is required	Not present
Optical system (light source + optics)	Not present	Requires cleaning of optical surfaces and occasional alignment; aging of light source affects sensitivity needing eventual replacement
Detector (PMT)	Not present	The signal can drift over time. Requires recalibration needing eventual replacement
Fouling sensitivity	Low	High
Typical performance issues	Sensitivity loss (typically nebulizer-related)	Increased baseline noise, drift, spiking and sensitivity loss (nebulizer, drift tube, dirty optics, aging light source)
Maintenance burden	Low	High

Case studies

We evaluated the performance of the CAD and the ELSD in four case studies. Collectively, the results demonstrated that the CAD provided superior performance, offering higher sensitivity, greater accuracy, improved robustness, and enhanced ease of use compared with the ELSD.

Case study #1: Liposome composition

Liposomes are small, spherical vesicles composed of one or more phospholipid bilayers that can encapsulate aqueous or lipid-soluble substances. They are often used for drug delivery, including cancer therapeutics (e.g., liposomal doxorubicin and liposomal irinotecan) and vaccines. ASTM International, formerly known as the American Society for Testing and Materials, is a globally recognized organization that develops and publishes technical standards for materials, products, systems, and services. These standards promote safety, quality, reliability, and consistency across a wide range of industries.

Two ASTM standard methods are available for the analysis of lipids in liposome formulations, with the detection limits (LODs), quantitation limits (LOQs), and quantitation range presented in Table 5:

- ASTM E3323-22: Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High-Performance Liquid Chromatography (HPLC) with an ELSD.[7]
- ASTM E3297-21: Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High-Performance Liquid Chromatography (HPLC) with a CAD.[8]

The CAD demonstrated superior sensitivity compared with the ELSD, providing lower LODs and LOQs, and a broader quantitative dynamic range. In addition, the ELSD method required detector-specific modifications to achieve optimal performance. One key difference was the required injection volume: the ELSD required a 15 µL injection, whereas the CAD required only 5 µL. Consequently, when sensitivity is expressed as mass on column, the sensitivity of the CAD is threefold greater than is apparent from the published concentration-based limits. For cholesterol, the difference in LOD is approximately 60-fold, with the ELSD detecting 24 ng on column compared with just 0.40 ng for the CAD.

The smaller injection volume required by the CAD also minimizes solvent-related chromatographic artifacts, such as peak broadening, tailing, and peak splitting associated with pure methanol injections. The resulting narrower, more symmetric peaks improve chromatographic resolution. This improvement is particularly important because resolving the two HSPC peaks has proven challenging with columns from some manufacturers, as demonstrated in a multi-site evaluation of the ASTM method.[9]

Case study #2: LNP composition

LNPs are widely employed as delivery vehicles for a range of therapeutics, including antisense oligonucleotides, siRNA-based drugs, mRNA vaccines, and small molecules. These formulations typically contain four lipid classes: ionizable lipids, PEGylated lipids, helper lipids, and cholesterol, although their precise compositions are often proprietary. The CAD is particularly well suited for quantifying these components because they generally lack chromophores.[10] For analyte identification, some analytical platforms incorporate mass spectrometry (MS), which can be coupled either through a diverter valve that alternates flow between the detectors or through a passive flow split that enables simultaneous CAD and MS detection.[11,12]

The Vanquish CAD P, paired with the Thermo Scientific™ Vanquish™ Horizon UHPLC System, was compared to a UHPLC-ELSD instrument for LNP sample testing. Instrumentation and chromatographic conditions are shown in Appendix 2. Four lipids were tested: PEG, cholesterol, distearoylphosphatidylcholine (DSPC), and an unknown. Similar analyte patterns were obtained for both detectors; however, the CAD achieved much lower LODs. Figure 4 illustrates the lowest concentration at which the PEG peak can be reliably integrated using the ELSD, corresponding to a signal-to-noise ratio (SNR) of 21. At this same concentration, the CAD produces an SNR of 527, demonstrating its substantially greater sensitivity. Figure 5 compares the calculated LODs and shows that the CAD was 12- to 47-fold more sensitive than the ELSD for this application.

Table 5. LODs, LOQs, and quantitation ranges for three lipids from model liposomes according to standard test methods for ASTM E3323-22 and ASTM E3297-21.

	Cholesterol LOD (µg/g)	Cholesterol LOQ (µg/g)	Cholesterol quantitation range (µg/g)
ELSD, ASTM E3323-22	2.0	10.0	10–165
CAD, ASTM E3297-21	0.1	1.0	5–300

	DSPE-PEG 2000 LOD (µg/g)	DSPE-PEG 2000 LOQ (µg/g)	DSPE-PEG 2000 quantitation range (µg/g)
ELSD, ASTM E3323-22	4.0	7.3	10–300
CAD, ASTM E3297-21	2.0	5.0	5–300

	HSPC LOD (µg/g)	HSPC LOQ (µg/g)	HSPC quantitation range (µg/g)
ELSD, ASTM E3323-22	2.0	7.6	10–200
CAD, ASTM E3297-21	2.0	5.0	5–300

DSPE-PEG 2000:1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000]
HSPC: hydrogenated soy phosphatidylcholine

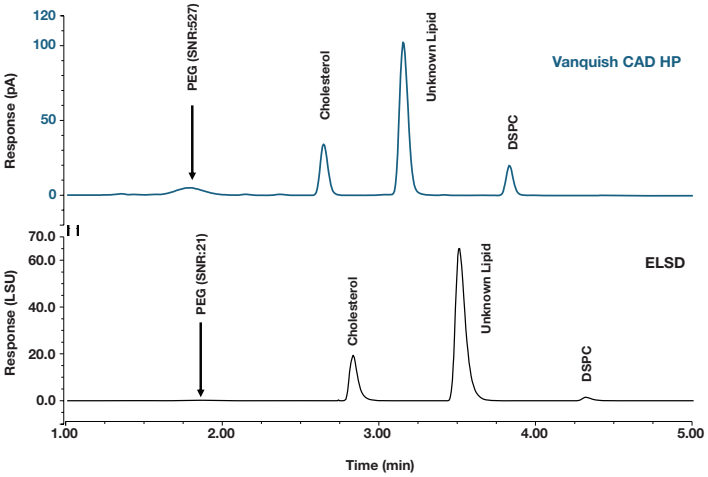


Figure 4. Comparison of the CAD (top) and the ELSD (bottom) for LNP sample testing. Lower levels for PEG could not be detected by ELSD. SNR are presented for PEG. *Note: Discrepancies in gradient delay volume of the LC systems resulted in retention time shifts apparent in the chromatograms.*

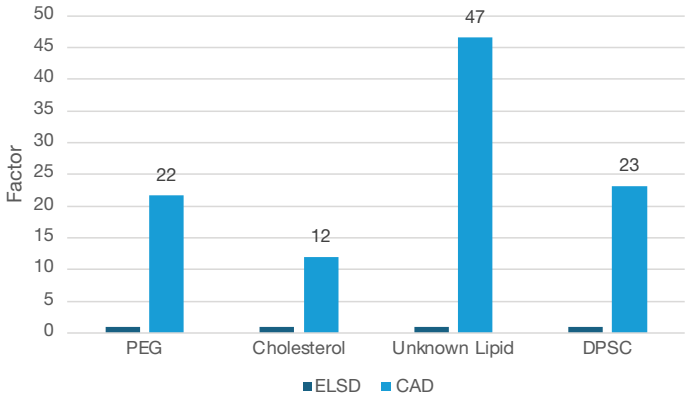


Figure 5. Comparison of the CAD vs. ELSD LODs for the four lipids in the LNP samples demonstrated by the factor of sensitivity increase.

Case study #3: Surfactant characterization

PS are nonionic surfactants widely used in pharmaceutical and biopharmaceutical formulations. They are inherently complex materials, comprising hundreds of individual molecular species arising from variability in both the starting materials and the manufacturing process. Consequently, their composition can vary between suppliers and even among production batches from the same supplier.

PS 80 is commonly characterized by reversed-phase high-performance liquid chromatography (RP-HPLC) using either an ELSD or the CAD.[13] Its chromatographic profile is complex, consisting of numerous small, narrow peaks together with a few large, broad peaks. This requires a detector that can accurately measure both peak types. For easier interpretation, the chromatogram is typically divided into four major peak groups (Figure 6).

Figure 6 compares chromatograms obtained with an ELSD and the CAD under identical column loading conditions. The CAD provided superior performance, detecting more species in peak groups 1 and 3 and produced higher responses for species in groups 2, 3, and 4. In addition, the CAD exhibited lower baseline noise, resulting in higher signal-to-noise ratios and improved overall detection sensitivity.

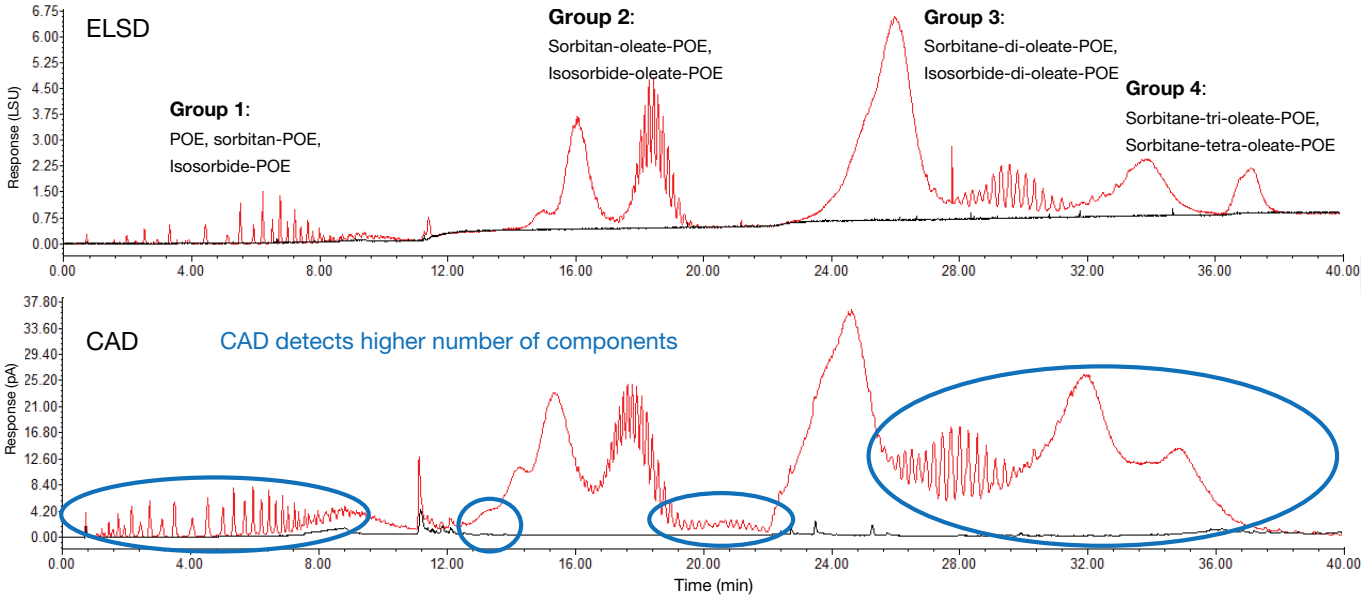


Figure 6. Chromatographic profiles of a PS 80 sample (1 mg/mL) obtained by the CAD and an ELSD. The water blank is shown in black. *Note: Discrepancies in the gradient delay volumes of the two LC systems resulted in retention time shifts apparent in the chromatograms. Method details can be found in Appendix 3.*

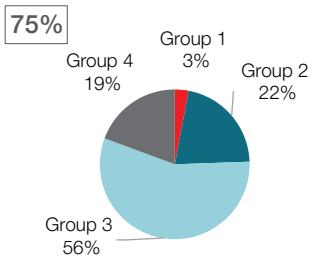
The CAD offers major advantages during method development. Unlike the ELSD, which requires optimization of multiple detector parameters, the CAD has fewer adjustable settings, simplifying method development (Table 3). Robustness studies further demonstrated that the CAD performance was minimally affected by changes in EvapT, whereas the ELSD responses were sensitive to changes in nebulizer temperatures (Figure 7). Notably, changes in the ELSD nebulizer temperature affected the responses of the PS groups to different extents, altering relative peak areas and potentially compromising quantitation. In contrast, changes in the CAD settings produced consistent responses across all PS groups, supporting more robust and reliable quantitation (Figure 7). The drift tube temperature is a critical parameter that must be evaluated during method development. The ELSD required a significantly higher drift tube temperature than the CAD evaporation tube temperature to minimize baseline noise and spiking caused by incomplete evaporation of the mobile phase. This higher operating temperature may explain the lower peak area observed for group 4 with the ELSD compared with the CAD, as the elevated temperature could result in greater loss of semi-volatile components.

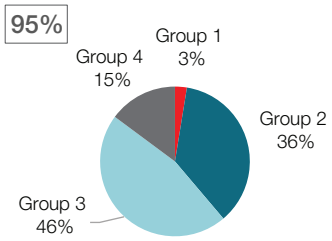
Case study #4: Impurity measurement

During manufacturing, PS can become contaminated with impurities such as fatty acids (FAs). Additionally, PS present in drug formulations may undergo degradation during storage and transportation, resulting in the generation of additional FAs. This is a significant concern because FAs can promote the formation of insoluble particles, potentially compromising product quality, therapeutic performance, and patient safety. Consequently, accurate quantification of FAs in both raw materials and finished drug products is essential. Since FAs lack suitable chromophores, they cannot be readily detected by conventional HPLC-UV methods without derivatization. Consequently, HPLC coupled with the CAD has become the preferred approach for the routine analysis of FAs.[14,15]

The Vanquish CAD P Series, paired with the Vanquish Horizon UHPLC System, was compared to a UHPLC-ELSD setup. Instrumentation and chromatographic conditions are shown in Appendix 4. Using a four–fatty acid standard mix under comparable conditions, both detectors showed a similar peak pattern (Figure 8), but the CAD delivered superior detection sensitivity, especially for the semi-volatile compound lauric acid. The CAD achieved a 10× higher SNR, highlighting its clear performance advantage.

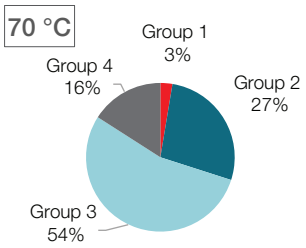
A ELSD, Nebulizer heating

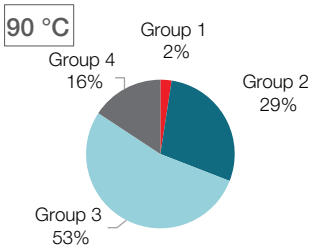




Group	1	2	3	4
Δ relative peak area [%]	0	+14	-10	-4

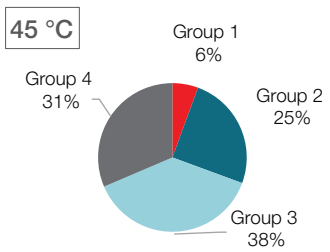
B ELSD, Drift tube temp.

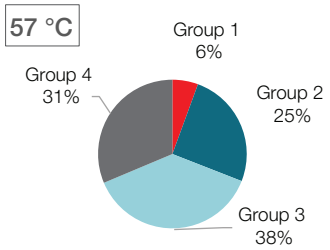




Group	1	2	3	4
Δ relative peak area [%]	-1	+2	-1	0

C CAD, Evaporation tube temp.





Group	1	2	3	4
Δ relative peak area [%]	0	0	0	0

Figure 7. Impact of instrument settings on robustness. For the ELSD, only the nebulizer temperature affected the results, as reflected by changes in relative peak areas for several groups (highlighted in red, A). In contrast, the ELSD drift tube temperature (B) had minimal impact, and the CAD evaporation tube temperature (C) had no impact on relative peak areas. For the ELSD, nebulizer heating is presented as a % (10% is equivalent to a change of 6 °C).

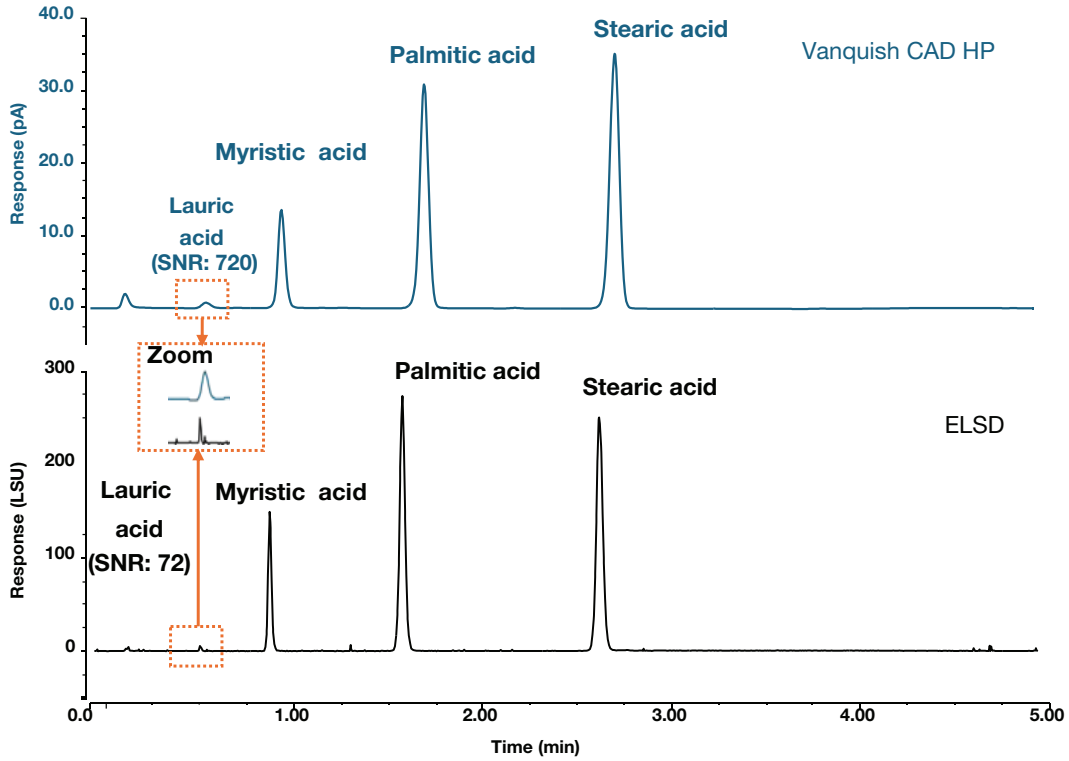


Figure 8. Comparison of CAD (top) and ELSD (bottom) analysis of fatty acid standard (50 µg/mL each) shows the CAD being 10 times higher in SNR for lauric acid. *Note: Differences in the gradient delay volume of the two LC systems resulted in minor shifts in retention times.*

Key considerations for modernization

The decision to retain an ELSD method or transition to the CAD should consider both analytical performance and the effort required to develop, operate, and maintain the method. A validated ELSD method that consistently meets its analytical requirements may remain fit for purpose, and in such cases the benefits of redevelopment and revalidation may not justify the effort.

However, analytical performance alone does not fully reflect method suitability. An ELSD method may generate acceptable results while requiring extensive detector optimization, multiple sample dilutions, repeated injections, or frequent maintenance. These additional activities consume analyst time, reduce laboratory throughput, and increase opportunities for variability. Where such challenges exist, transferring the method to the CAD can improve both analytical performance and operational efficiency.

Method transfer should be considered when greater sensitivity is required for low-level components or impurities, when samples contain analytes spanning a wide concentration range, or when detector settings have a significant impact on method performance. The CAD also improves method robustness and reproducibility across instruments, analysts, laboratories, and development and quality control environments.

Instrument replacement and lifecycle planning provide an ideal opportunity to evaluate method modernization. Rather than replicating the limitations of an existing ELSD workflow, laboratories can assess whether the CAD offers a simpler, more robust approach with greater confidence in analytical results and better support for future applications.

For new methods requiring universal detection, the CAD is the detector of choice. Its higher sensitivity, wider dynamic range, reduced need for detector-specific optimization, and simpler operation facilitate method development, routine use, and transfer. These advantages are particularly valuable for complex pharmaceutical and biopharmaceutical samples containing non-chromophoric compounds, low-level impurities, or analytes present over a broad concentration range.

In summary, ELSD methods that remain fit for purpose can continue to be used effectively. However, where existing workflows are limited by complexity, sensitivity, or robustness, transitioning to the CAD provides significant analytical and operational benefits. For new universal detection methods, the CAD should generally be considered the preferred detector.

Conclusion

The CAD provides a more capable universal detection platform for pharmaceutical and biopharmaceutical applications than the ELSD. Across the applications evaluated, the CAD demonstrated advantages that improve both analytical performance and laboratory efficiency via:

- Lower detection limits
- Greater confidence in low-level impurity measurement
- More consistent response across diverse analyte classes
- A broader working range, reducing dilutions and repeated analyses
- Less method optimization and simpler operation
- Lower routine maintenance requirements

These benefits are particularly relevant for complex formulations, including liposomes, lipid nanoparticles, surfactants, and biopharmaceutical excipients. While established ELSD methods may remain fit for purpose, the CAD should be considered the preferred platform for new methods and for workflows being modernized to improve sensitivity, robustness, quantitation, and productivity.

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Appendix 1 - Detector response characteristics and effect on performance

For the CAD, the relationship between signal response and particle diameter (d) is straightforward. For particles of d = 10 nm to 1.0 µm, the mean charge per particle is proportional to $d^{1.133}$ (giving a wide quasi-linear response and wide dynamic range). If d < 10 nm, then the response is proportional to $d^{2.25}$ (resulting in signal drop off).[16]

For the ELSD, the relationship between signal response and particle diameter is considerably more complex, exhibiting a sigmoidal profile due to the combined influence of three light-scattering mechanisms. This behavior depends on the ratio d/λ, where λ represents the wavelength of the incident light. For λ = 500 nm:

Refraction/reflection: d > 1.0 µm proportional to d^2

Mie: d = 50 nm to 1.0 µm proportional to d^4

Rayleigh: If d < 50 nm proportional to d^6

Larger d transition (50 vs. 10 nm) and higher exponents (4 and 6) underline the poorer detection limits and more complex response curves of the ELSD. This well-established physical dependency applies to all ELSD instruments.

Response can be defined by a power function:

$$A = a(m_{inj})^b$$

Where m_{inj} is the analyte mass injected, *a* indicates the overall sensitivity, and b describes the curve shape. For example, when *b* = 1, the response is linear.

A comparison of the response curves for the ELSD and the CAD is shown in Figure 9.

For the CAD:

- Detection limits extend to lower mass levels since signal drop only occurs for <10 nm particles.
- Wider quasi-linear and dynamic ranges.
- Gradual changes in slope results in better precision.
- The combination of high sensitivity and broad dynamic range facilitates the simultaneous quantitation of the API and trace-level impurities, often at levels below 0.1% relative to the API peak, within a single analytical run, thereby reducing sample reanalysis and streamlining analytical workflows.
- LODs cannot be estimated from high standards.[1]

For the ELSD:

- Exponential signal drop at low mass range where smaller particles (< 50 nm) predominate. This can produce artificially sharp peaks (peak shaving) that may seem suitable for UHPLC but may lead to underestimation of the analyte concentration measured.[16,17]
- Narrow quasi-linear (b~1) and smaller dynamic range.
- Large changes in slope results in poorer precision.
- LODs cannot be estimated from high standards.[1]

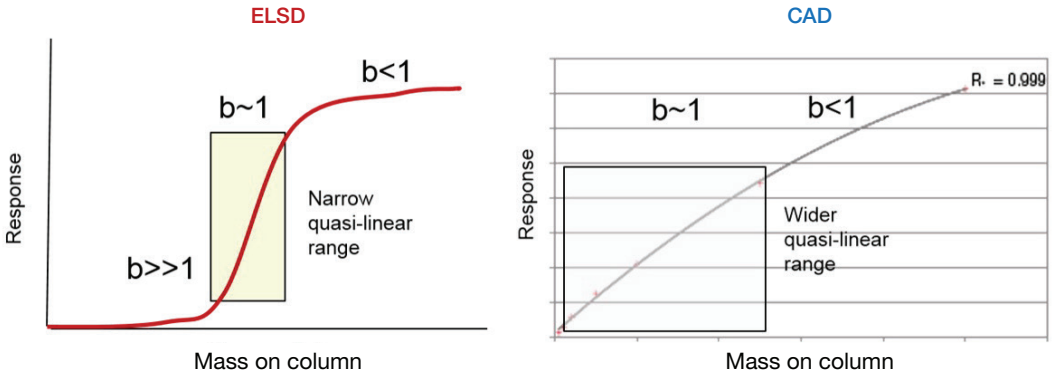


Figure 9. Response curves for ELSD and CAD. Linear if b = 1.0; Sublinear if b < 1; Supralinear if b > 1.

Appendix 2 - LNP analysis

Chemicals

Product	Cat. No.
Fisher Chemical™ Optima™ Formic Acid, LC/MS grade	A117
Fisher Chemical™ Optima™ Ammonium Formate, LC/MS grade	A115
Fisher Chemical™ Optima™ Acetonitrile, LC/MS grade	A955
Fisher Chemical™ Optima™ Isopropanol (2-Propanol), LC/MS grade	A461
Fisher Chemical™ Optima™ Methanol, LC/MS grade	A456
Fisher Chemical™ Optima™ Methanol, HPLC grade	A454

Sample handling

Product	Cat. No.
Thermo Scientific™ SureSTART™ 2 mL GOLD-Grade Glass Screw and Crimp Top Vials, Level 3	6PSV9-1PG
Thermo Scientific™ SureSTART™ 9 mm Blue Polypropylene AVCS™ Screw Caps with Soft Blue Silicone/Clear PTFE Septa, 100/pack, Level 3	6PSC9ST101

Instrumentation

ELSD system	CAD system	Cat. No.
Non-Vanquish quaternary UHPLC system	Thermo Scientific™ Vanquish™ Horizon UHPLC System with UV (DAD HL) and CAD consisting of:	
	Thermo Scientific™ Vanquish™ System Base	VF-S01-A-03
	Thermo Scientific™ Vanquish™ Binary Pump H	VH-P10-A-02
	Thermo Scientific™ Vanquish™ Split Sampler HT	VH-A10-A-03
	Thermo Scientific™ Vanquish™ Column Compartment H	VH-C10-A-03
ELSD	Thermo Scientific™ Vanquish™ Charged Aerosol Detector HP	VH-D21-A-01
Empower 3 FR5 SR3.7	Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) 7.3.1	

Chromatographic conditions

Column	C18 column, 2.1 mm x 100 mm, 1.7 µm	
Solvent A	50% 12.5 mM Ammonium acetate, 50% methanol	
Solvent B	50% Methanol, 50% isopropanol	
Gradient	**Time [min]**	**B [%]**
	0	75
	1	75
	3	85
	3.5	85
	4	75
	5	75
Flow rate	0.75 mL/min	
Column temperature	70 °C	
Active pre-heater temperature	On, 70 °C	
Autosampler temperature	15 °C	
Injection volume	5 µL	
CAD settings	Data collection rate: 10 Hz Filter setting: 2.0 s PV: 1.8 Evaporation temperature: 35 °C Temperature Coupling Mode: Off	
ELSD settings	Data collection rate: 10 Hz Nebulizer mode: Heating 58% (35 °C) Drift tube temp. 40 °C Gain: 50 Gas pressure: 25 psi	

Appendix 3 – Polysorbate analysis

Chemicals, sample handling, and instrumentation: *See Appendix 2.*

Column	Thermo Scientific™ Accucore™ C18, 150 x 2.1 mm, 2.6 µm (Cat. No. 17126-152130)	
Solvent A	5 mM Ammonium formate in ultrapure DI water	
Solvent B	50% Acetonitrile, 50% isopropanol	
Gradient	**Time [min]**	**B [%]**
	0	9
	3	9
	10	22
	10	57
	21	69
	21	84
	26	85
	35	100
	45	100
	46	9
	56	9
Flow rate	0.4 mL/min	
Column temperature	50 °C	
Active pre-heater temperature	Not Used	
Autosampler temperature	10 °C	
Injection volume	10 µL	
CAD settings	Data collection rate: 20 Hz Filter setting: 3.6 s PV: 1.5 Evaporation temperature: 50 °C Temperature coupling mode: Off	
ELSD settings	Data collection rate: 5 Hz Nebulizer mode: Heating 85% (51 °C) Drift tube temp. 80 °C Gain: 100 Gas pressure: 30 psi	

Appendix 4 - Impurity measurement

Chemicals, sample handling, and instrumentation: *See Appendix 2.*

Chromatographic conditions

Column	Thermo Scientific™ Hypersil GOLD™ C18 Selectivity 50 x 2.1 mm; 1.9 µm (Cat. No. 25002-052130)	
Solvent A	0.05% Formic acid in ultrapure DI water (v/v)	
Solvent B	0.05% Formic acid in acetonitrile (v/v)	
Gradient	**Time [min]**	**B [%]**
	0	75
	1	75
	3	85
	3.5	85
	4	75
	5	75
Flow rate	0.75 mL/min	
Column temperature	25 °C	
Active pre-heater temperature	Off	
Autosampler temperature	6 °C	
Injection volume	10 µL	
CAD settings	Data collection rate: 10 Hz Filter setting: 2.0 s PV: 1.8 Evaporation temperature: 35 °C Temperature Coupling Mode: Off	
ELSD settings	Data collection rate: 10 Hz Nebulizer mode: Heating 58% (35 °C) Drift tube temp. 40 °C Gain: 50 Gas pressure: 25 psi	

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