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HPLC-Charged Aerosol Detection

Excipients applications notebook
Complex substances, universal chromatographic analysis

Thermo Fisher SCIENTIFIC

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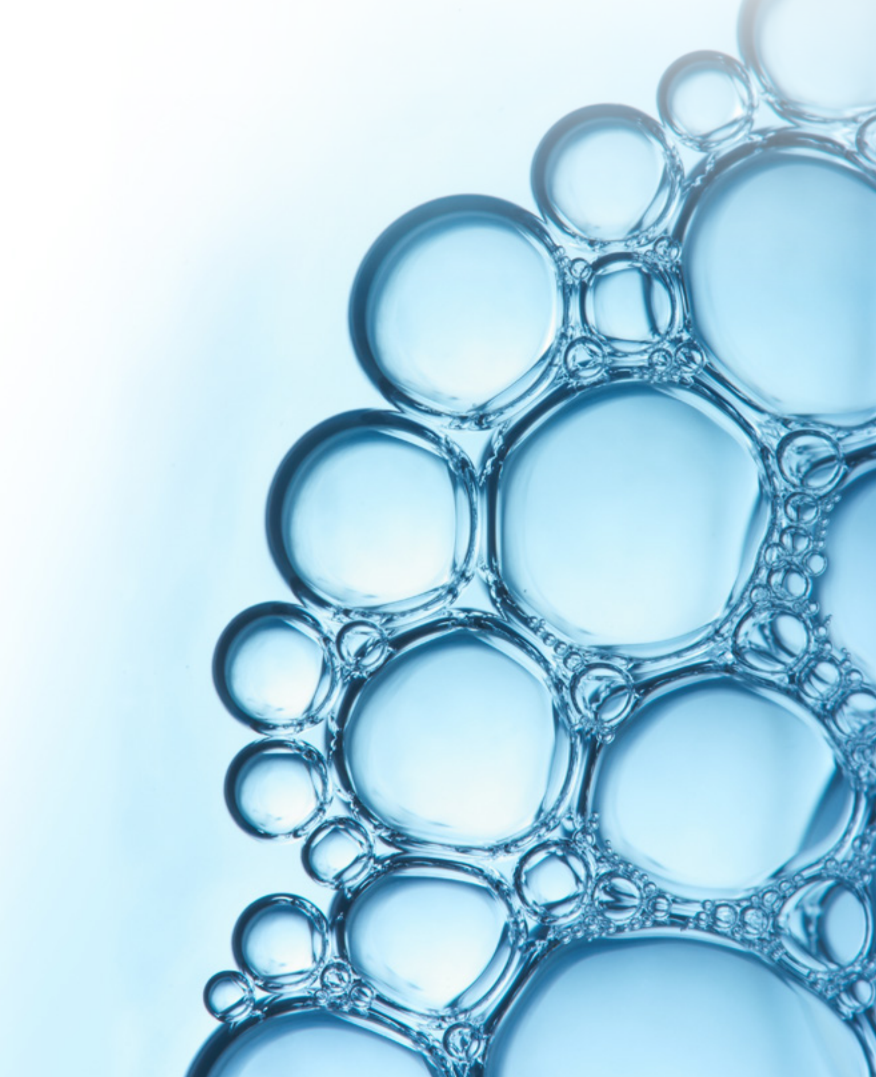
The analysis of excipients and impurities comes with several challenges.

1. Separation: Structures of the impurities are mainly hydrophilic and ionic, requiring special separation techniques like mixed-mode chromatography.

2. Detection: Analytes lacking a chromophore are not detected by optical detectors, which are the main devices used in pharmaceutical monographs.

3. Quantitation: Reference standards are often not available for excipients and their related substances.

This notebook offers a summary of applications and helpful information as to how high performance liquid chromatography combined with a charged aerosol detector can be used to meet the needs of scientists working with excipients and active pharmaceutical ingredients or when impurity profiling is needed.



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Overview

The word excipient originates from the Latin *excipere*, which means to receive i.e., the excipient receives the active substance. The European Pharmacopoeia (Ph. Eur.) 4 states: “An excipient is any component, other than the active substance(s), present in a medicinal product or used in the manufacture of the product”. Excipients include substances that facilitate powder flowability or non-stick properties during manufacturing. In the drug product, they may act as bulking agents, fillers, or diluents, or are used to enhance drug absorption, reduce viscosity, enhance solubility, or prevent denaturation or aggregation over the expected shelf life. Other excipients such as sweeteners modify the taste of a medicine and contribute to improving patient compliance. Colors enable the identification of medicines and help to decrease the risk of patients mistaking one product for another. The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors.

Vaccines, in addition to weakened or killed disease antigens, also contain very small amounts of an excipient called an adjuvant. This excipient helps to promote the effectiveness of a vaccine by reducing the amount or frequency of the required dose, by prolonging the duration of immunological memory, or by modulating the involvement of humoral or cellular responses.

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Excipient function

The intended function of an excipient is to guarantee the required physicochemical and biopharmaceutical properties of the pharmaceutical preparation. Excipients play a number of roles including:

- Adjuvant
- Aerosol propellant
- Antifoaming
- Antimicrobial preservatives
- Antioxidant
- Binder
- Buffering agent
- Bulking agent (freeze-drying)
- Chelating/sequestering agent
- Coating agent
- Coloring, flavor, perfume
- Counterions
- Diluent
- Disintegrant
- Emulsifying/solubilizing/wetting agent
- Glidant, anticaking agent
- Humectant
- Lubricant
- Ointment/suppository base
- Plasticizer
- Powder flowability or non-stick properties
- Stiffening agent
- Surfactants
- Suspending/viscosity-increasing agent
- Sweetening agent
- Tonicity agent
- Vehicle
- Viscosity control

For more information: The central role of excipients in drug formulation

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Measurement

Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. They, therefore, consist of a wide range of substances with diverse chemical structures and can be challenging to analyze.

Many excipients lack a chromophore and cannot be measured using HPLC High Performance Liquid Chromatography (HPLC) with UV/Vis detection. However, as they are typically non-volatile, they are good candidates for determination by charged aerosol detection.

Thermo Scientific™ UHPLC-Charged Aerosol Detector (CAD) systems, with state of the art column technologies, along with proven analytical methods, precise automation and advanced data handling will help you to:

- Quantify excipients
- Estimate the quantity of analytes for which individual standards are not available
- Analyze excipients in a broad range of samples

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CAD – Universal detection

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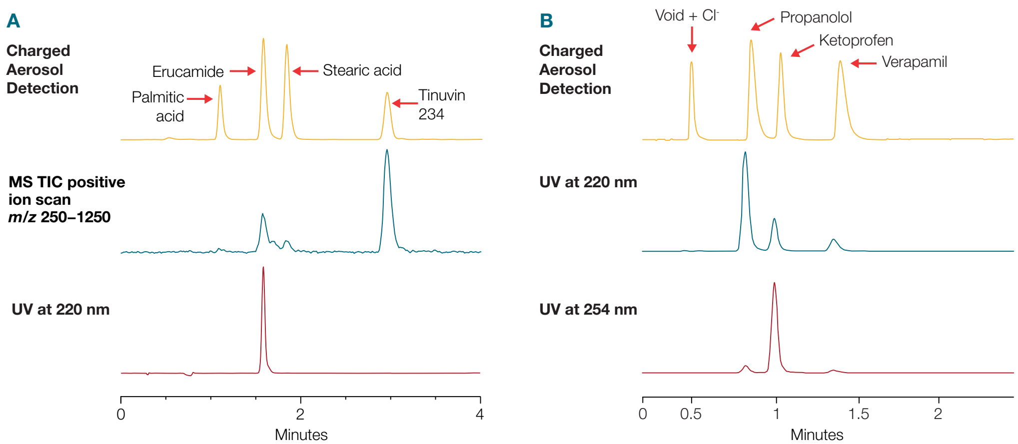

The CAD can measure all analytes in the two samples shown above. Other detectors are more limited in scope. For example, MS requires that analytes form gas phase ions (A) while response by a UV detector depends upon the nature of the chromophore (A and B).

The analyte detection challenge

No single detection method delivers ideal results for LC analysis. Often, one analyte responds more strongly to a detection method than another, or it may not respond at all. What is most desired is the ability to detect a wide range of analytes (universal detection) with a response that enables accurate quantitation. Charged aerosol detection is a reliable technology that will change the way you view every sample. The CAD can detect all non-volatile, and many semi-volatile analytes, with uniform response for non-volatiles. Charged aerosol detection has the flexibility and performance for analytical R&D, as well as the simplicity and reproducibility needed for QA/QC in manufacturing. It can be used for the analysis of pharmaceuticals (large and small molecule), biomolecules, food and beverages, specialty chemicals and polymers.

Learn more: Discover what you're missing – CAD brochure

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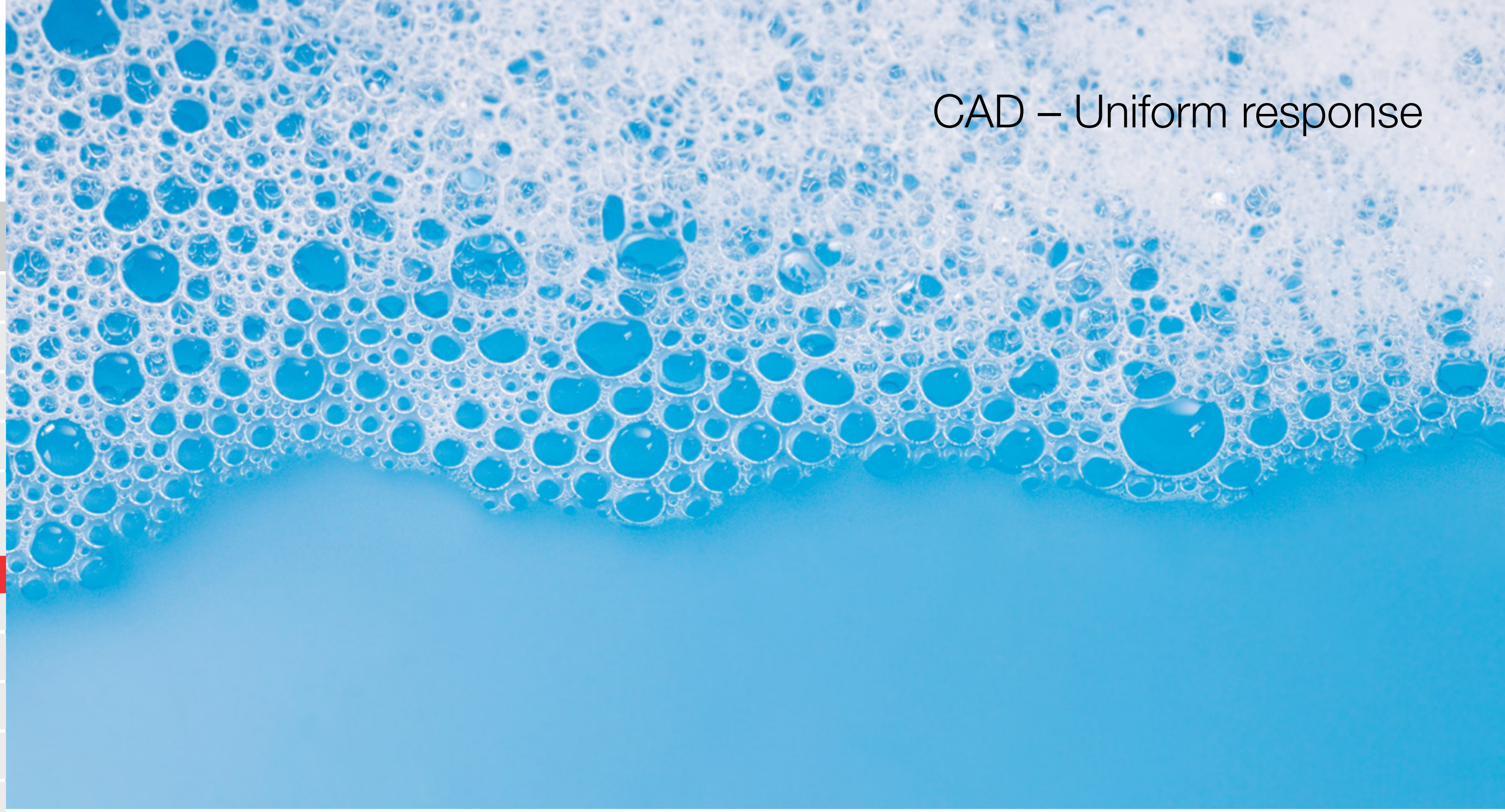
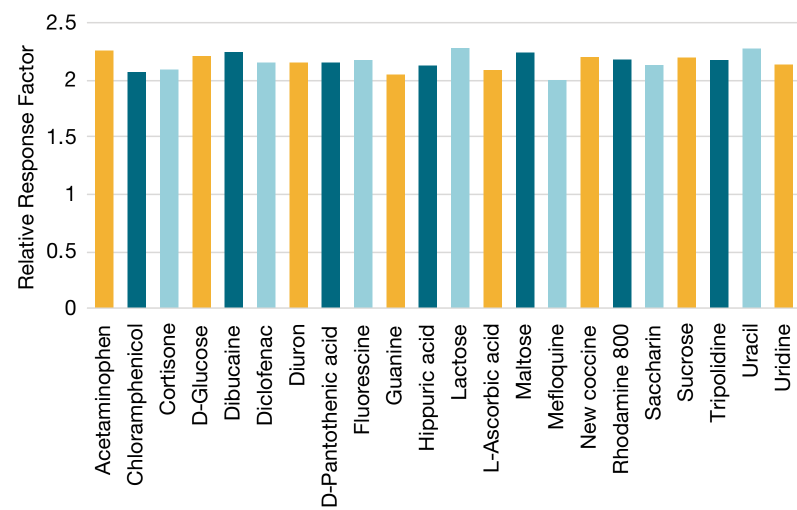


CAD – Uniform response

Uniform response with charged aerosol detection

- Detector response is independent of analyte structure for all non-volatile compounds
- Excellent sensitivity coupled with wide dynamic range for unrivaled performance
- Single calibrant for quantification of multiple analytes when individual standards are not available
- Facilitating easy single or total amount determination of heterogeneous excipients like surfactants



The CAD shows uniform response (<5% RSD variation) for all non-volatile analytes (0.5 µg on column; flow injection analysis).

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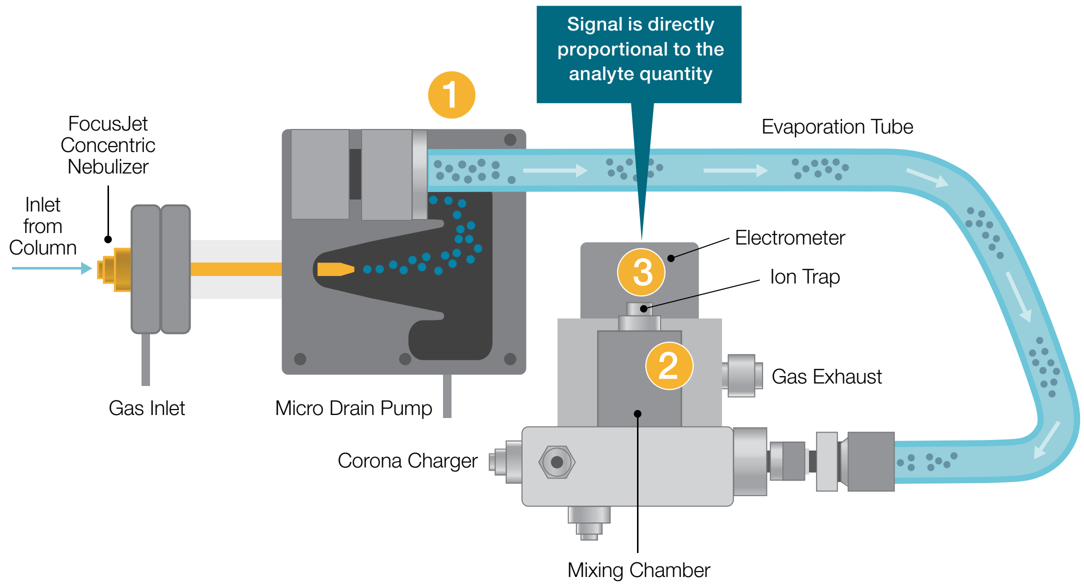

Schematic of CAD technology

Three simple steps to charged aerosol detection

1. Nebulization
Charged aerosol detection begins by nebulizing the column eluent into droplets, which are subsequently dried into particles. The particle size increases with the amount of analyte.

2. Charging
In the mixing chamber a stream of ionized nitrogen gas collides with the analyte particles. The charge is then transferred to the particles—the larger the particle, the greater the charge.

3. Detection
The charged particles are transferred to a collector where the aggregate charge is measured by a highly sensitive electrometer. This generates a signal directly proportional to the quantity of analyte present.

Learn more: Charged Aerosol Detection Technology

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CAD – Modules

Laboratories need state-of-the art instrumentation to competently analyze excipients with charged aerosol detection.

Thermo Scientific™ UHPLC systems combined with Thermo Scientifc™ Charged Aerosol Detectors (CAD), with advanced column technologies, and with proven analytical methods provide you precise automation and advanced data handling to help you:

- Characterize many classes of excipients
- Analyze compounds in a broad range of samples
- Profile or quantify analytes

Thermo Scientific™ Vanquish™ Charged Aerosol Detectors and Thermo Scientific™ Corona™ Veo™ Charged Aerosol Detectors provide:

- Simple, intuitive operation
- Wide linear and dynamic range
- Sub-nanogram sensitivity
- Method flexibility covering micro-flow HPLC and UHPLC applications with a single nebulizer
- Adjustable evaporation temperature to optimize signal-to-noise ratio

Learn more: Discover what you're missing – CAD brochure

Vanquish Charged Aerosol Detector

Corona Veo Charged Aerosol Detector

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General purpose and specialty columns

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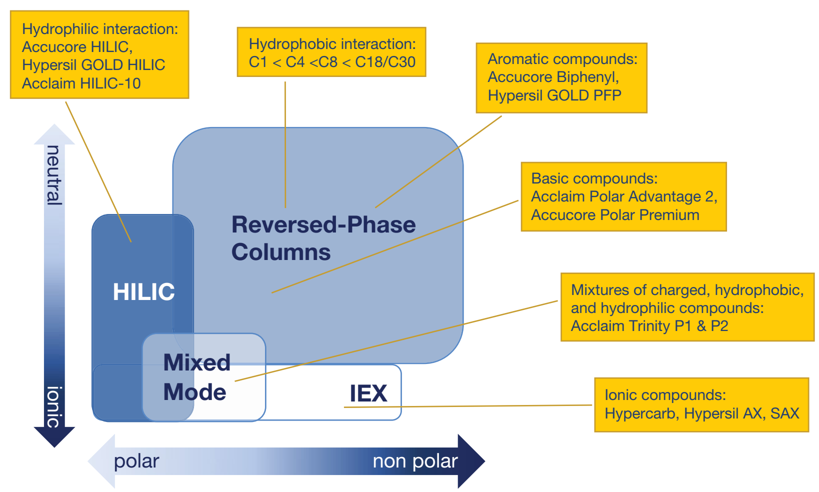
Superior results achieved through high quality columns

Excipient analysis can encompass a wide variety of analytes. The more you know about your sample, the easier it will be to select the best chemistry for separation. Thermo Scientific offers a wide range of bonded phases, particle sizes, particle morphologies and column dimensions to meet any application need so you can achieve maximum resolution for your excipients, active pharmaceutical ingredients (APIs) or impurity profiling analyses.

When selecting a column, the first step to consider is sample load. Both the Thermo Scientific™ Hypersil™ GOLD column family and Thermo Scientific™ Acclaim™ column family are fully porous, allowing for high resolution of complicated sample matrices and large injection volumes. In cases of limited sample volume, the Thermo Scientific™ Accucore™ column family should be selected. Accucore consists of superficially porous (solid core) particles that provide greater signal-to-noise with smaller injection volumes or for UHPLC separations without elevated system backpressure.

For most analytes, the hydrophobic properties of the column governs the separation. Please keep the following rules of thumb in mind when selecting a column:

- While C18 is the most common phase selected in method development, consider hydrophobic retention trends with the carbon load on the column: C1 < C4 < C8 < C18 / C30. In the case of highly aliphatic hydrocarbons (lipids), the Thermo Scientific™ Acclaim™ C30 columns and Thermo Scientific™ Accucore™ C30 columns offer greater selectivity with shorter run times compared to a traditional C18.
- Select a wider pore silica column (Thermo Scientific™ Acclaim™ 300 C18 column or Thermo Scientific™ Accucore™ 150 C18 column) to minimize sample carryover when working with compounds of large molecular weight (>4kDa).
- Achieve greater retention of moderately polar analytes (including basic compounds) by selecting a polar embedded column, such as the Thermo Scientific™ Acclaim™ PA2 column or Thermo Scientific™ Accucore™ Polar Premium column.
- Enhance steric selectivity and resolution of aromatic compounds with phenyl based columns, including the Thermo Scientific™ Accucore™ Biphenyl column or Thermo Scientific™ Hypersil™ GOLD PFP column
- Separate APIs from counter-ions with the Thermo Scientific™ Acclaim™ Trinity P1 column and Thermo Scientific™ Acclaim™ Trinity P2 column. Engineered to provide controlled ion exchange and RP/HILIC properties, the Trinity line works well for samples that show a mix of ion exchange and hydrophobic/hydrophilic properties.



Adjuvants – AbISCO-100™

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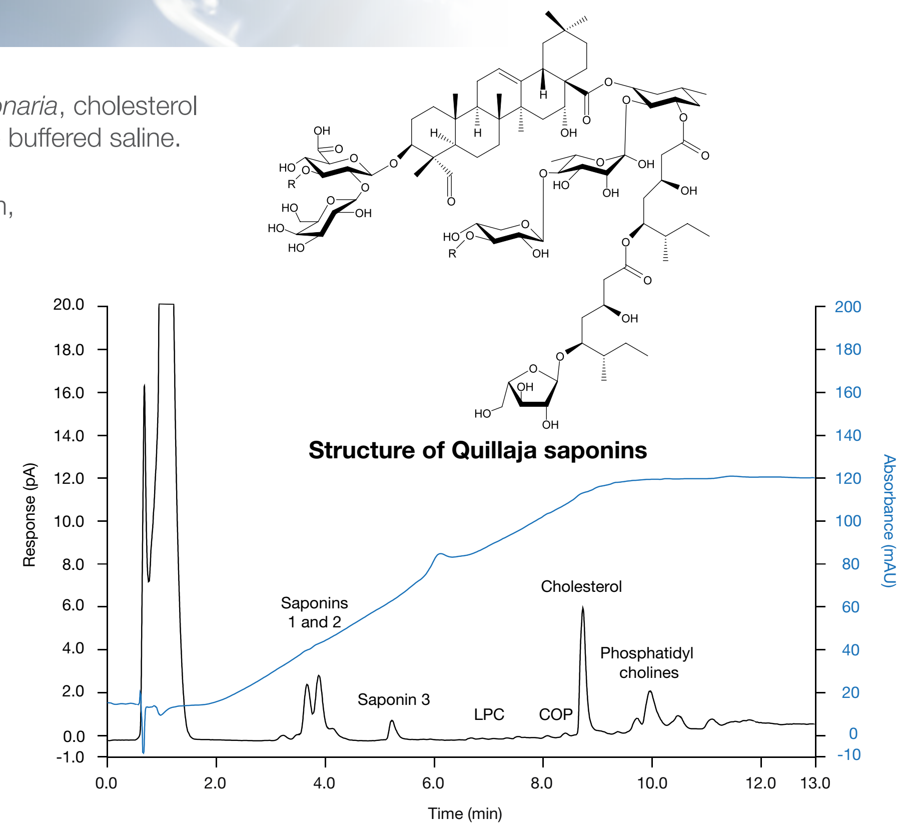
AbISCO-100 is a suspension of purified saponins from *Quillaja saponaria*, cholesterol from sheep wool and egg phosphatidyl cholines (PCs) in phosphate buffered saline.

HPLC column:	Thermo Scientific Hypersil GOLD PFP, 1.9 µm, 2.1 × 100 mm
Mobile phase A:	0.1% Formic Acid in DI Water
Mobile phase B:	0.1% Formic Acid in 10:90 Acetonitrile: Ethanol
Column temperature:	45 °C
Flow rate:	0.47 mL/min
Injection volume:	10 µL
Gradient:	See Table
Detectors:	Charged Aerosol and UV (220 nm)

Time (min)	%A	%B
-5	65	35
0	65	35
7	20	80
12	20	80



ABISCO-100™ (ISCONOVA, Uppsala Sweden) was diluted 5-fold with Milli-Q® water prior to analysis. All components and several degradation products including cholesterol oxidation products (COP) and lyso-PC (LPC) were detected by the charged aerosol detector, but showed limited response by UV detection.

Download Poster Note: Direct Analysis of Multicomponent Adjuvants by HPLC with Charged Aerosol Detection

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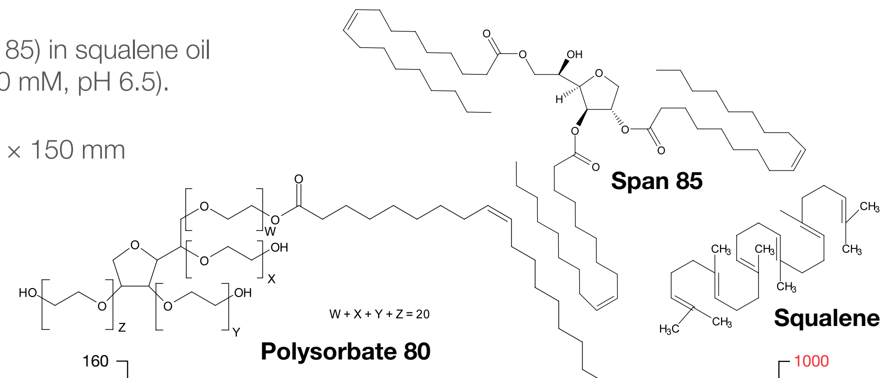
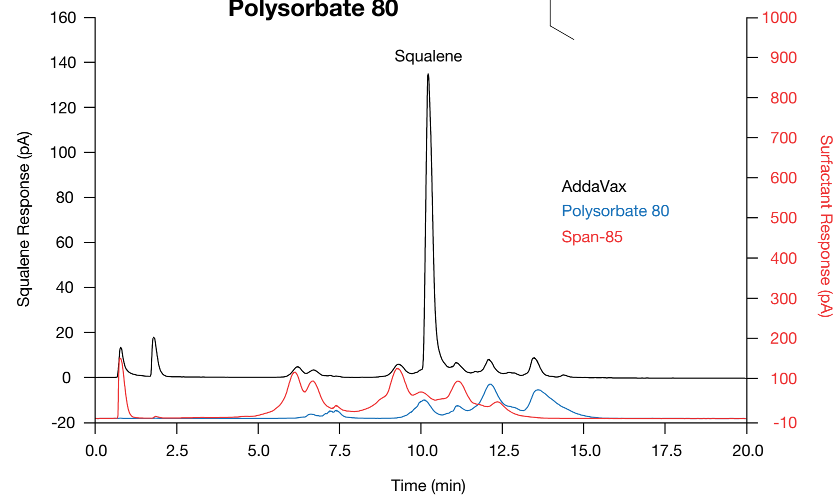
Adjuvants – Addavax™

AddaVax is prepared by emulsification of sorbitan trioleate (SPAN™ 85) in squalene oil (5% v/v) and polysorbate 80 (0.5% w/v), in sodium citrate buffer (10 mM, pH 6.5).

HPLC column: Thermo Scientific Accucore C8, 2.6 µm, 4.6 × 150 mm
Mobile phase A: 1 mM Ammonium Acetate in DI Water
Mobile phase B: Isopropanol
Column temperature: 40 °C
Flow rate: 0.8 mL/min
Injection volume: 10 µL
Gradient: See table
Detector: Charged Aerosol

Time (min)	%A	%B
0	35	65
3	35	65
13	10	90
18	10	90
18.1	35	65
30	35	65





AddaVax was diluted 10-fold with water prior to analysis by UHPLC-charged aerosol detection. Chromatograms for other AddaVax components are also shown.

Download Poster Note: Direct Analysis of Multicomponent Adjuvants by HPLC with Charged Aerosol Detection

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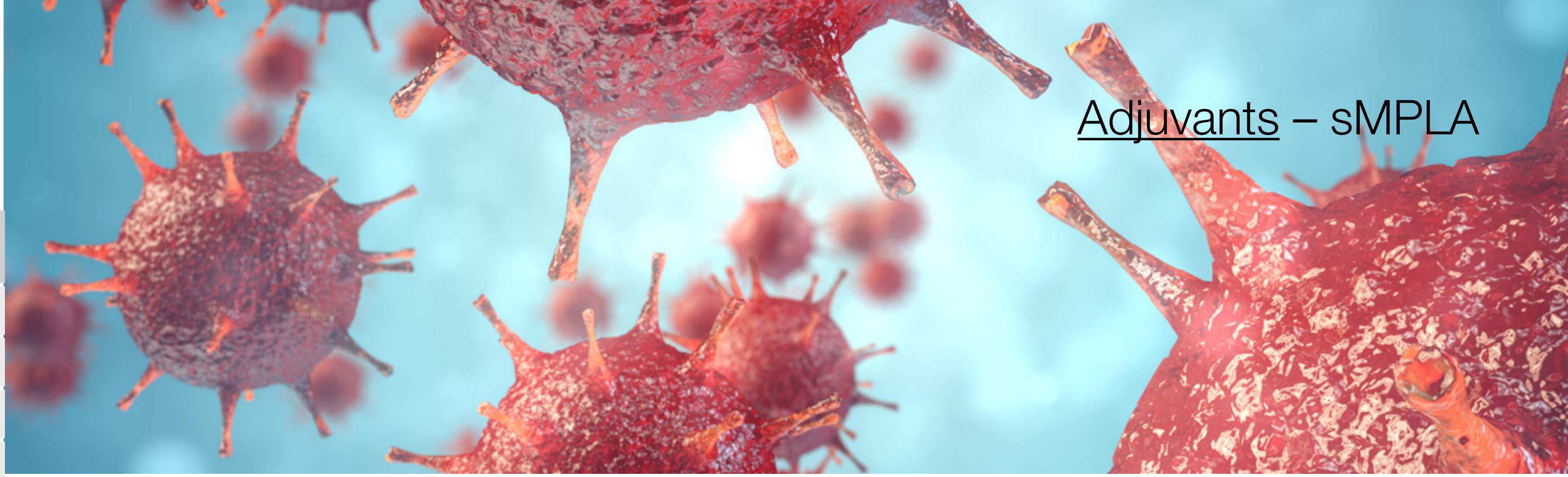
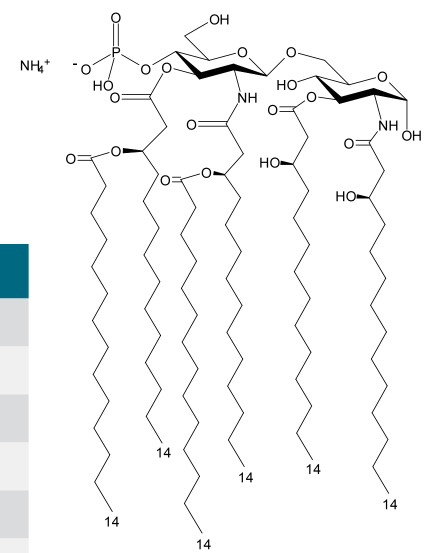


Adjuvants – sMPLA

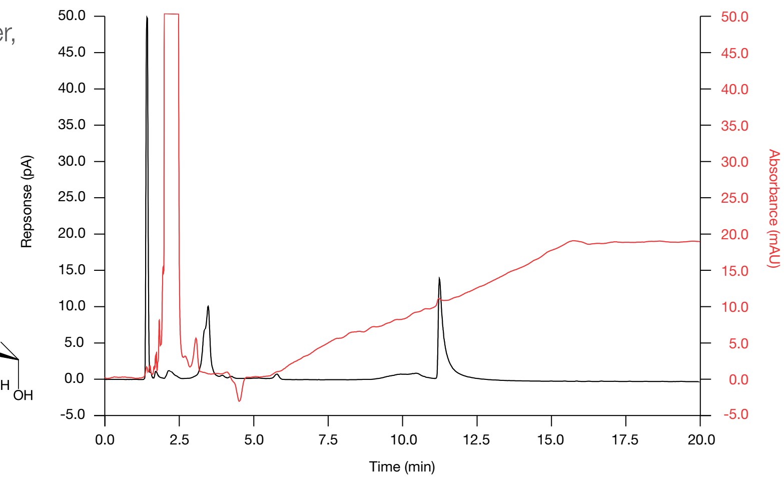
Synthetic monophosphoryl lipid A (sMPLA) (Avanti Polar Lipids, GA), a hexa-acyl analog of bacterial lipopolysaccharide, has low toxicity while specifically activating toll-like receptor 4 (TLR4) but not TLR2. Purity analysis is used to quantify contaminants, degradation products, and variants differing in acyl chain number, length, and phosphorylation.

HPLC column:	Thermo Scientific Accucore C8, 2.6 µm, 4.6 × 150 mm
Mobile phase A:	1 mM Ammonium Acetate in DI Water
Mobile phase B:	Isopropanol
Column temperature:	40 °C
Flow rate:	0.8 mL/min
Injection volume:	10 µL
Gradient:	See table
Detectors:	Charged Aerosol and UV (220nm)

Time (min)	%A	%B
0	35	65
3	35	65
13	10	90
18	10	90
18.1	35	65
30	35	65



Monophosphoryl lipid A



Purity analysis of sMPLA by HPLC-UV-charged aerosol detection. sMPLA was dissolved in chloroform:methanol:water 80:20:4 at a concentration of ~1 mg/mL prior to analysis. (Black trace – CAD; red trace – UV).

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Amino acids

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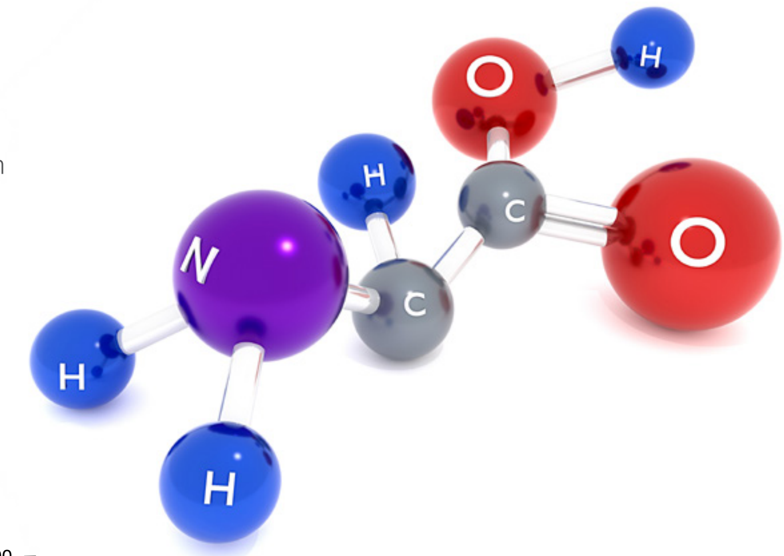
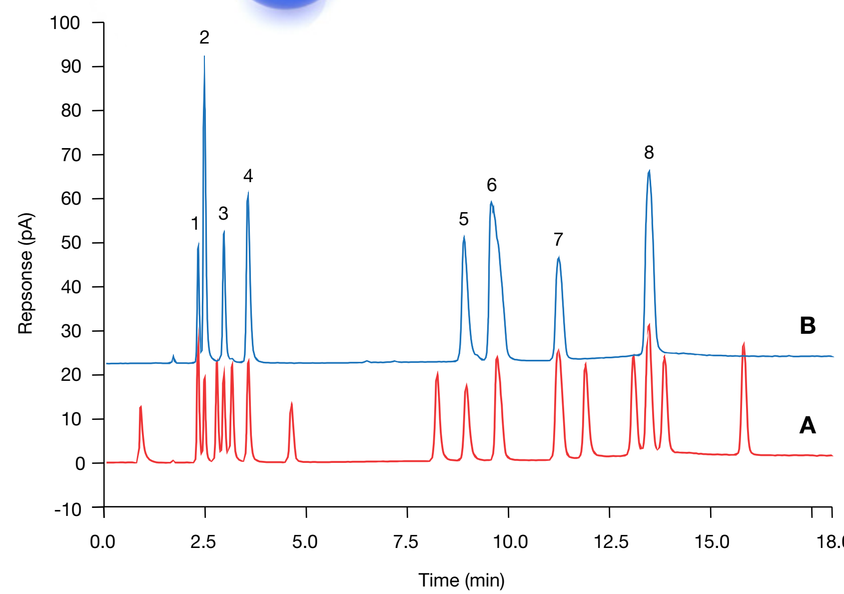


HPLC column: Thermo Scientific Acclaim PA2, 2.2 µm, 2.1 × 250 mm
Mobile phase A: 0.15% Nonafluoropentanoic acid in DI Water
Mobile phase B: 0.2% Trifluoroacetic acid in Acetonitrile
Mobile phase C: 5% Acetic Acid
Column temperature: 40 °C
Flow rate: See table
Injection volume: 10 µL
Gradient: See table
Detector: Charged Aerosol

Time (min)	Flow Rate (mL/min)	%A	%B	%C
0.0	0.4	90	2	8
1.0	0.4	90	2	8
2.5	0.5	92	3	5
10.0	0.5	89	8	3
14.0	0.5	80	18	2
19.0	0.5	68	30	2
24.0	0.5	68	30	2
25.0	0.5	89	3	8



Direct analysis of underivatized amino acids by UHPLC-CAD. A) Pierce amino acid standard H. B) Amino acids typically used as excipients. 1 – Aspartate; 2 – Glycine; 3 – Glutamate; 4 – Proline; 5 – Methionine; 6 – Histidine; 7 – Lysine; 8 – Arginine.

See Poster Note: Characterization of a Biologic Therapeutic: Reversed Phase Analysis of Protein and Excipients

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Carbohydrates – simple sugars

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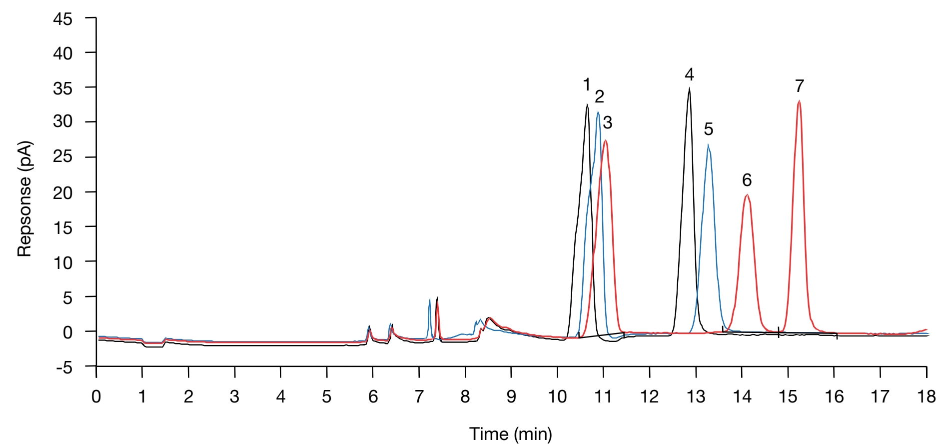
HPLC column: HILIC
Mobile phase A: 20 mM Ammonium Acetate, 5% Acetic acid
Mobile phase B: Methanol
Mobile phase C: Acetonitrile
Column temperature: 50 °C
Flow rate: See table
Injection volume: 2 µL
Gradient: See table
Detector: Charged Aerosol

Time (min)	Flow Rate (mL/min)	%A	%B	%C
0.00	0.50	5	0	95
1.35	0.50	5	0	95
1.35	0.50	12	15	73
1.90	0.85	12	15	73
11.00	0.85	12	33	55
16.00	0.50	12	33	55
18.00	0.50	5	0	95



Direct analysis of simple carbohydrates by UHPLC-CAD. 1 – Sorbitol; 2 – Mannitol; 3 – Glucose; 4 – Sucrose; 5 – Lactose; 6 – Mannose; 7 – Trehalose.

See Poster Note: Determination of Proteins and Carbohydrates by 2D HPLC (RPLC and HILIC) with Charged Aerosol and Ultraviolet Detection

Further information for carbohydrate analysis is provided in following resources:
Label-Free Analysis by UHPLC with Charged Aerosol Detection of Glycans Separated by Charge, Size and Isomer
Label-Free Profiling of O-linked Glycans by HPLC with Charged Aerosol Detection
Direct Measurement of Sialic Acids Released From Glycoproteins, by HPLC and CAD
Carbohydrate Analysis using HPLC with PAD, FLD, Charged Aerosol Detection, and MS Detectors

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Carbohydrates – cyclodextrin

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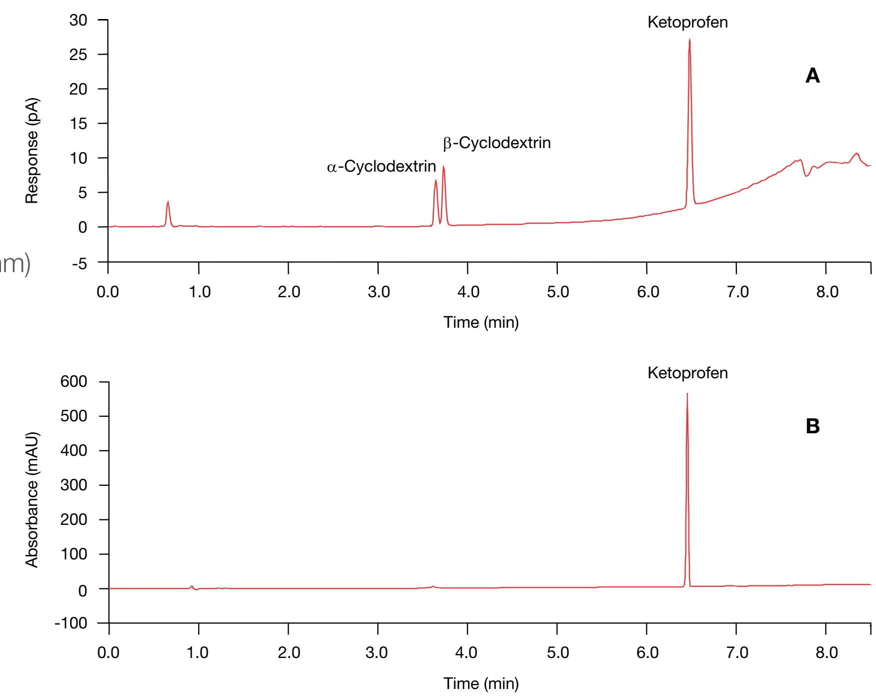
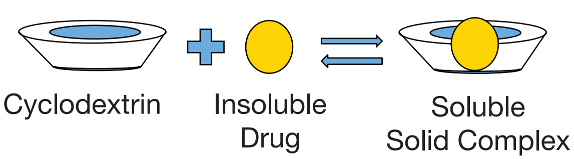
HPLC column:	Thermo Scientific Acclaim PA2, 2.2 µm, 2.1 × 250 mm
Mobile phase A:	0.1% aq Formic Acid
Mobile phase B:	Acetonitrile, 0.1% Formic Acid
Column temperature:	40 °C
Flow rate:	0.7 mL/min
Injection volume:	10 µL
Gradient:	See table
Detectors:	Charged Aerosol and UV absorbance (254 nm)

Time (min)	%A	%B
0.0	100	0
2.0	100	0
7.0	10	90
8.0	10	90
8.5	100	0
11.0	100	0



Analysis of cyclodextrins and Ketoprofen using UHPLC with CAD (A) and UV (B).



See Poster Note: Multi-Modal Analyte Detection of Cyclodextrin and Ketoprofen Inclusion Complex

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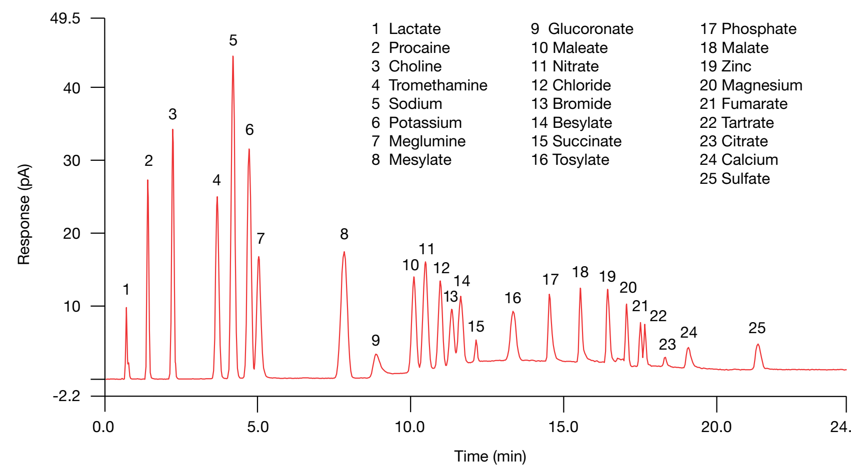
Counterions – global method

HPLC column:	Thermo Scientific Acclaim Trinity P1, 3 µm, 3 × 50 mm
Mobile phase A:	DI Water
Mobile phase B:	Acetonitrile
Mobile phase C:	200mM Ammonium Formate, pH 4.0
Column temperature:	35 °C
Flow rate:	0.5 mL/min.
Injection volume:	10 µL
Gradient:	See table
Detector:	Charged Aerosol

Time (min)	% B	% C	Gradient Curve
0	60	3	5
7	60	5	4
15	5	90	7
23	5	90	5
23.1	60	3	5
28	60	3	5



Global method for measurement of anions, cations, organic and inorganic ions simultaneously.

See Poster Note: Monitoring of Anions and Cations in Early Stage Product Formulation
Also:
Acclaim Trinity P1 Columns Product Manual
Acclaim Trinity P2 Columns Product Manual
A Platform Method for Pharmaceutical Counterion Analysis by HPLC

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Counterions – API and counterion

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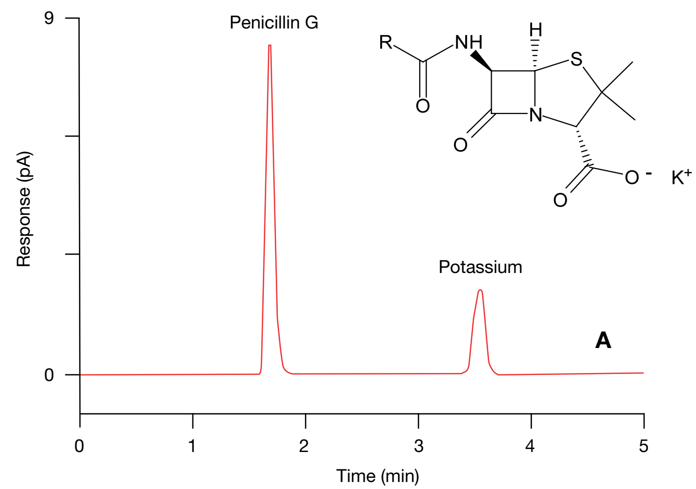
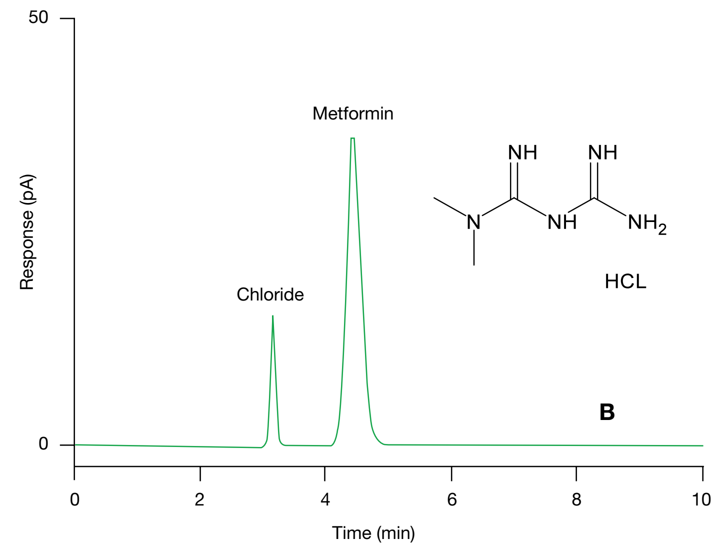
HPLC column:	Thermo Scientific Acclaim Trinity P2, 3 µm, 3 × 50 mm
Mobile phase A:	Acetonitrile
Mobile phase B:	DI Water
Mobile phase C:	100 mM Ammonium Formate, pH 3.65
Column temperature:	30 °C
Flow rate:	0.5 mL/min
Injection volume:	1 µL
Isocratic:	25:50:25 (v/v) A:B:C
Detector:	Charged Aerosol

HPLC column:	Thermo Scientific Acclaim Trinity P2, 3 µm, 3 × 50 mm
Mobile phase A:	Acetonitrile
Mobile phase B:	100 mM Ammonium Formate, pH 3.65
Column temperature:	30 °C
Flow rate:	0.5 mL/min
Injection volume:	1 µL
Isocratic:	80:20 (v/v) A:B
Detector:	Charged Aerosol





Analysis of Penicillin G Potassium Salt (A) and Metformin Chloride (B) by UHPLC-CAD.

Download: A Platform Method for Pharmaceutical Counterion Analysis by HPLC

More applications on this area can be found here:

API and Counterions in Adderall Using Multi-Mode Liquid Chromatography with Charged Aerosol Detection

Separation of Calcium, Magnesium and Counterions in a Dietary Supplement Using Multi-mode Liquid Chromatography

Acclaim Trinity P1 Columns Product Manual

Acclaim Trinity P2 Columns Product Manual

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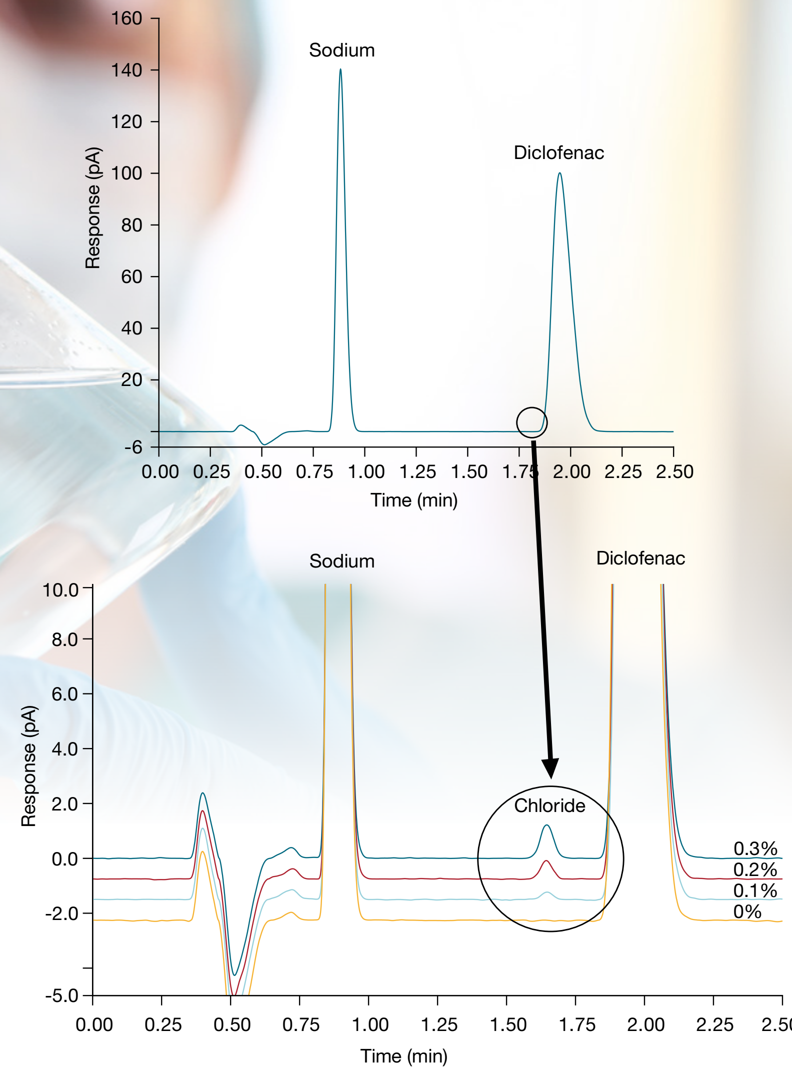
Counterions – API, counterion and trace impurity measurement



Analysis of diclofenac sodium salt (1 mg/mL) by UHPLC-CAD showing ability to measure chloride impurity at the 0.1% level (lower trace shows the upper chromatogram presented at higher sensitivity).

HPLC column:	Acclaim Trinity P1, 3 µm, 3.0 × 50 mm
Mobile phase A:	75% Acetonitrile
Mobile phase B:	25% 200 mM Ammonium Acetate, pH 4
Column temperature:	30 °C
Flow rate:	0.8 mL/min
Injection volume:	5 µL
Detector:	Charged Aerosol

See:
Acclaim Trinity P1 Columns Product Manual (PN 065306)
Acclaim Trinity P2 Columns Product Manual (PN 065561)

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Nonionic surfactants

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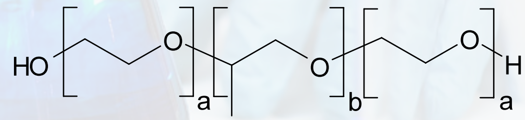
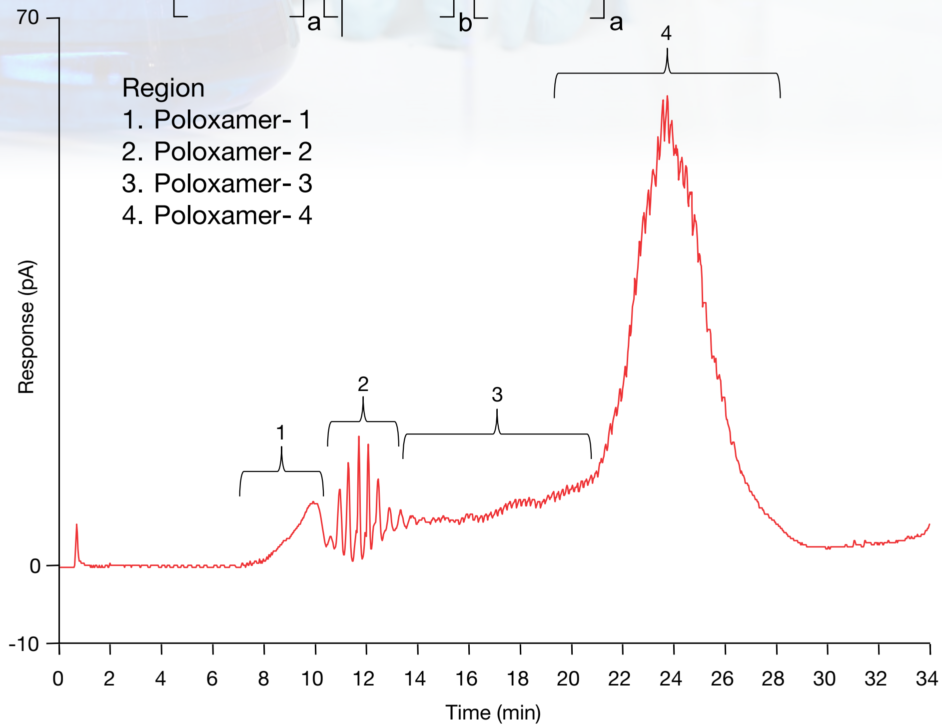
Poloxamers

HPLC column: Accucore Vanquish C18, 1.5 µm, 2.1 × 150 mm
Column temperature: 50 °C
Mobile phase A: Aqueous Acetonitrile 50% (v/v)
Mobile phase B: Tetrahydrofuran*
Mobile Phase C: Water
Flow rate: 0.4 mL/min
Gradient: See table
Injection volume: 2 µL
Detector: Charged Aerosol

Time (min)	%A	%B	%C	Curve
-6	50	0	50	—
0	50	0	50	5
3	50	0	50	5
25	25	50	25	4
33	5	90	5	5
34	50	0	50	5

*BHT free





Characterization of poloxamer 407 (Pluronic F127).

See Poster Note: Characterization and Lot-to-Lot Variability of Complex Surfactants by High Performance Liquid Chromatography and Charged Aerosol Detection

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Polysorbates – quantification

HPLC column: Thermo Scientific™ Betasil™ C1, 5 µm, 3.0 × 100 mm

Column temperature: 30 °C, still air mode

Mobile phase A: DI Water

Mobile phase B: Acetonitrile/Methanol/Trifluoroacetic acid (28/70/2)

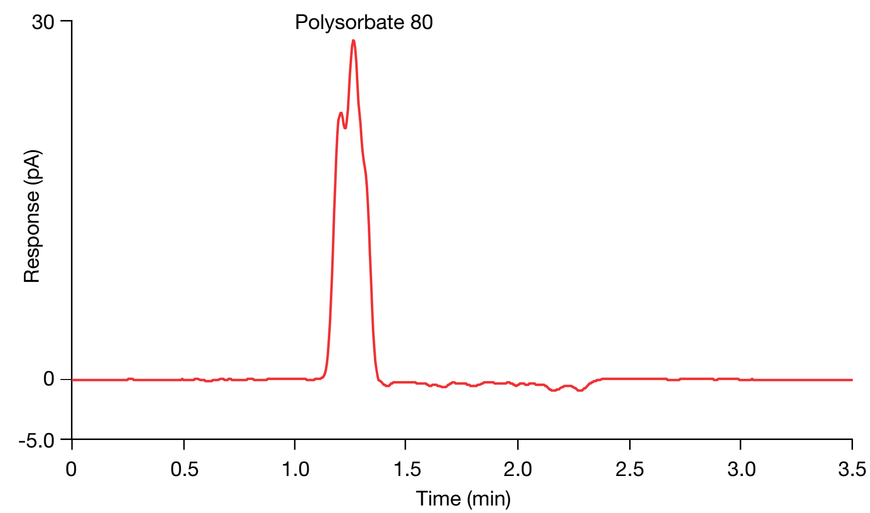
Flow rate: See table

Gradient: See table

Injection volume: 5 µL

Detection: Charged Aerosol Detector

Time (min)	Flow Rate (mL/min)	%A	%B
0	1.00	100	0
0.5	1.00	100	0
0.7	1.35	0	100
0.8	1.50	0	100
1.5	1.50	0	100
1.7	1.00	100	0
3.5	1.00	100	0



Elution of polysorbate 80 standard as a single peak for more sensitive quantification.

See Poster Note: Application of Charged Aerosol HPLC Detection in Biopharmaceutical Analysis

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Nonionic surfactants

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Polysorbates – material characterization

HPLC column: Acclaim 300 C18, 3 µm, 4.6 × 150 mm

Column temperature: 30 °C

Mobile phase A: Acetonitrile/Methanol/DI Water/Trifluoroacetic Acid (8/2/90/0.1)

Mobile phase B: Acetonitrile/Methanol/DI Water/Trifluoroacetic Acid (72/18/10/0.1)

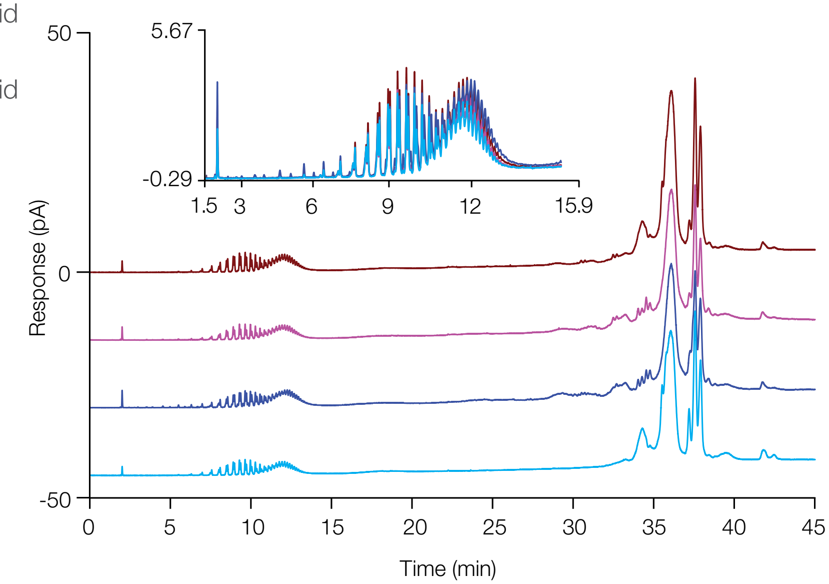
Flow rate: 0.4 mL/min

Gradient: See table

Injection volume: 2 µL

Detection: Charged Aerosol Detector

Time (min)	%A	%B
0	100	0
1	100	0
33	0	100
57	0	100
59	0	100
64	100	0



Determination of lot-to-lot variability. Stacked plot of four commercially available polysorbate 80 products. Low molecular weight components overlaid (Inset).

Download Poster Note: Evaluation of Methods for the Characterization and Quantification of Polysorbates and Impurities along with other Surfactants and Emulsifiers used in the Food and Pharmaceutical Industries

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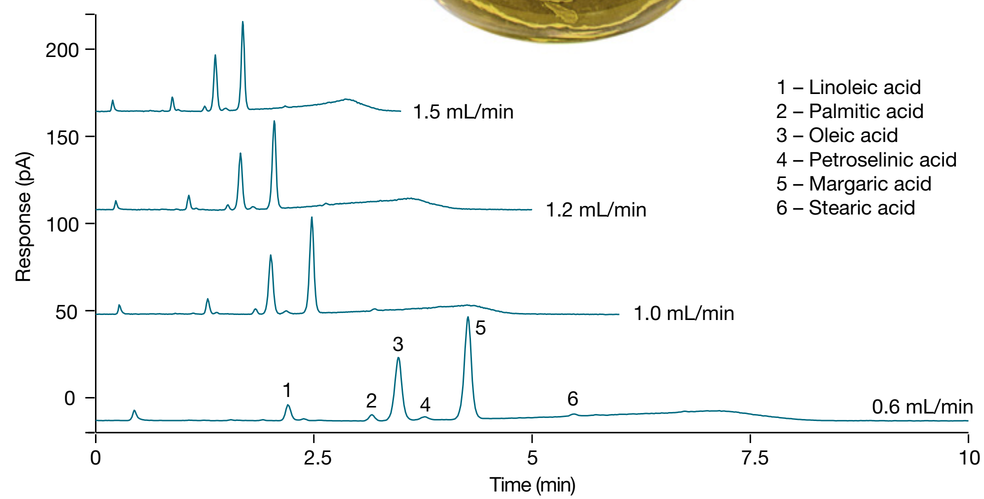
Polysorbates – Polysorbate 80 fatty acid impurity analysis

HPLC column: Core-shell C18, 2.6 µm, 2.1 × 100 mm
Column temperature: 25 °C, still air mode
Mobile phase A: 0.05% (v/v) Formic acid in DI water
Mobile phase B: 0.05% (v/v) Formic acid in Acetonitrile
Flow rate: 1.5 mL/min
Gradient: See table
Detection: Charged Aerosol Detector

Time (min)	%A	%B
0	25	75
0.8	25	75
2.5	15	85
3.0	15	85
3.5	25	75
4.5	25	75



We are grateful to Professor Dr. U. Holzgrabe (University of Würzburg) for providing this figure.

Chromatographic separation of different fatty acids found in polysorbate 80 hydrolysates using different flow rates. 1) linoleic acid; 2) palmitic acid; 3) oleic acid; 4) petroselinic acid; 5) margaric acid; and 6) stearic acid.

See Poster Note: Fatty Acid Analysis in Polysorbate 80 by UHPLC-CAD
Refer to article: Influence of charged aerosol detector instrument setting on the ultra-high-performance liquid chromatography analysis of fatty acids in polysorbate 80

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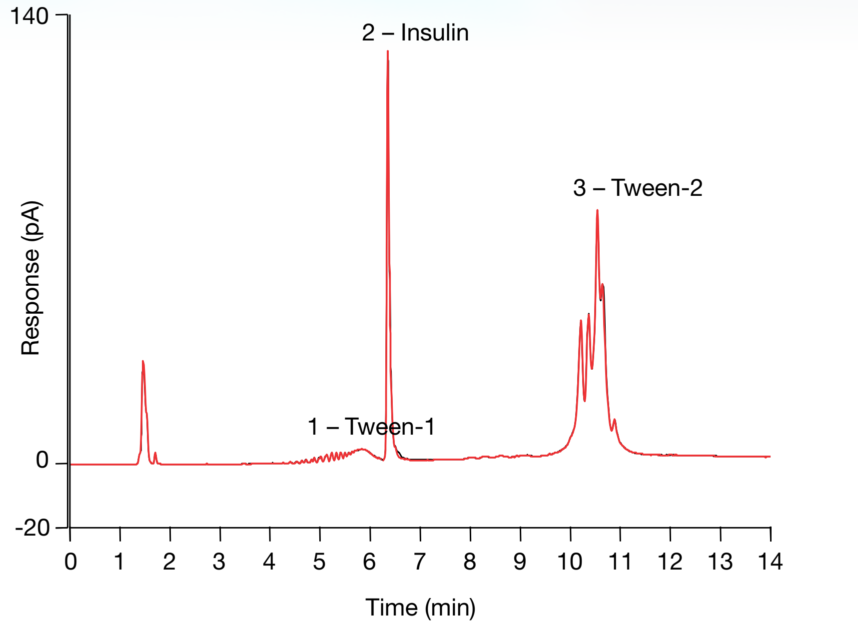
Polysorbates – Polysorbate 80 and insulin in a biopharmaceutical

HPLC column: Accucore 150-C4, 2.6 µm, 3 × 100 mm
Column temperature: 50 °C
Mobile phase A: 0.1% Trifluoroacetic acid
Mobile phase B: Acetonitrile, 0.1 v/v-% Trifluoroacetic acid
Mobile phase C: n-Propanol/Tetrahydrofuran* (80:20)
Flow rate: 0.5 mL/min
Gradient: See table
Injection volume: 20 µL
Detection: Charged Aerosol Detector

Time (min)	%A	%B	%C
-5	90	10	0
0	90	10	0
7	25	75	0
7.1	0	0	100
12	0	0	100
13	0	100	0
14	90	10	0

*BHT free



Simultaneous determination of peptide and surfactant in a biopharmaceutical.

For more information: HPLC-CAD analysis of polysorbate 80 and insulin in a biopharmaceutical formulation

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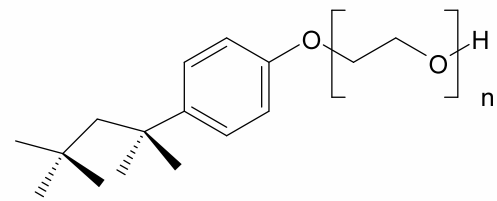
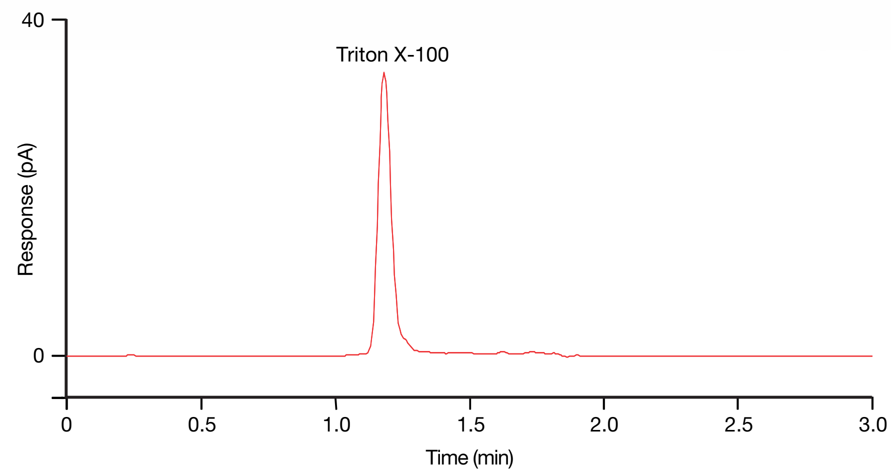
Triton X-100 – quantification

HPLC column:	Betasil C1, 5 µm, 3.0 × 100 mm
Column temperature:	30 °C, still air mode
Mobile phase A:	DI water
Mobile phase B:	Acetonitrile/Methanol/Trifluoroacetic acid (28/70/2)
Flow rate:	See table
Gradient:	See table
Injection volume:	5 µL
Detection:	Charged Aerosol Detector

Time (min)	Flow Rate (mL/min)	%A	%B
0	1.00	100	0
0.5	1.00	100	0
0.7	1.35	0	100
0.8	1.50	0	100
1.5	1.50	0	100
1.7	1.00	100	0
3.5	1.00	100	0





Elution of Triton X-100 standard as a single peak for more sensitive quantification.

See Poster Note: Application of Charged Aerosol HPLC Detection in Biopharmaceutical Analysis

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Polyethylene glycol

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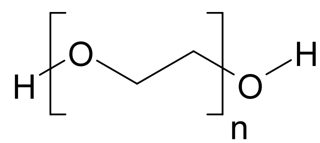
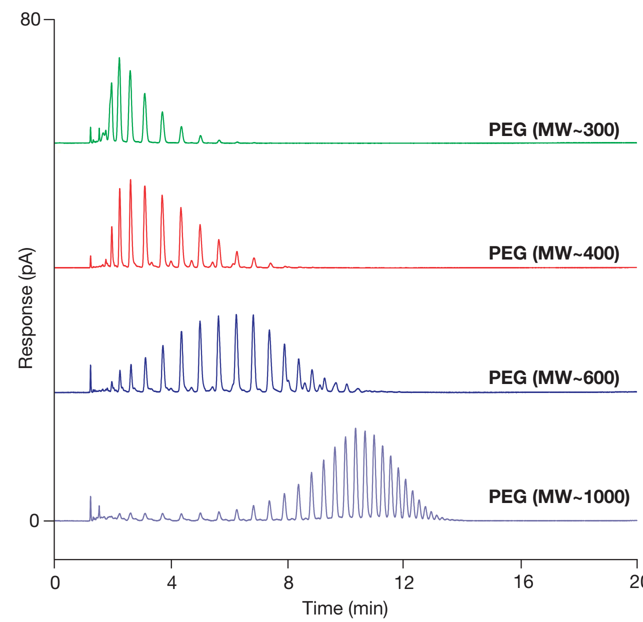
HPLC column: Acclaim Surfactant Plus, 3.0 µm, 3.0 × 150 mm
Column temperature: 30 °C
Mobile phase A: 100 mM Ammonium Acetate, pH 5.0
Mobile phase B: Acetonitrile
Flow rate: 0.6 mL/min
Gradient: See table
Injection volume: 5 µL
Detector: Charged Aerosol



Time (min)	%A	%B
-8	98	2
0	98	2
20	80	20



Characterization of different PEGs.

Learn more: HPLC charged aerosol detector analysis of polyethylene glycol (PEG)

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Simultaneous analysis of protein and excipients in biologics using 2D approaches

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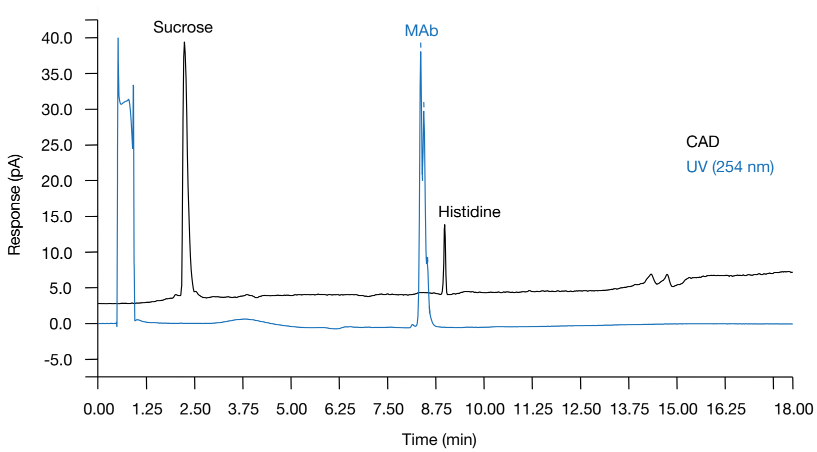
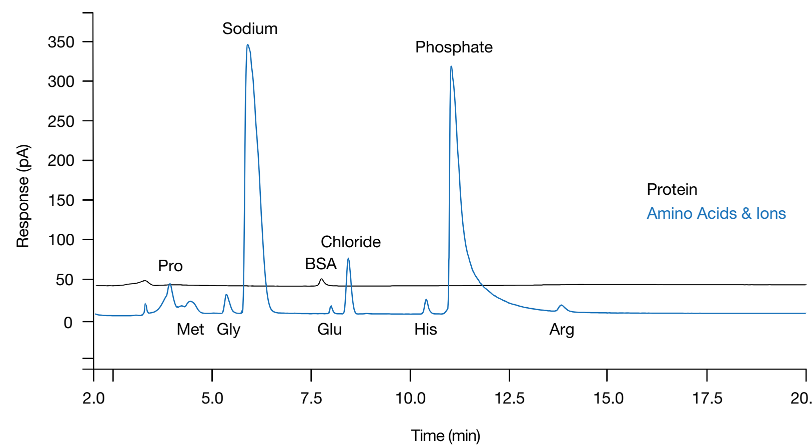
Analysis of a biologic formulation can be extremely challenging. Typically, separate methods are used to measure the biologically active protein and associated excipients. To improve laboratory efficiency with faster analysis times and less sample preparation, these methods can be combined into a 2D heart-cut HPLC approach.

In the example shown below (right figure) the protein was separated in the first dimension using an Accucore 150 C4 column and measured using a diode array detector. A heart cut (0.5 to 0.8 min) containing the polar amino acids was transferred to a second column via a switching valve. The separation of underivatized amino acid excipients and several ions was achieved using an Acclaim Trinity P1 column under HILIC conditions and measured using charged aerosol detection.



Analysis of commercial protein formulation with amino acid and carbohydrate excipients. For method conditions see: Characterization of a Biologic Therapeutic: Reversed Phase Analysis of Protein and Excipients.



Analysis of mock biologic containing protein and amino acid excipients by UHPLC-CAD. For method conditions see: 2D Analysis of Protein Therapeutics and Amino Acid Excipients with Combined UV and Charged Aerosol Detection.

For another example for the use of this approach see: Determination of Proteins and Carbohydrates by 2D HPLC (RPLC and HILIC) with Charged Aerosol and Ultraviolet Detection

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Adjuvant

Any substance that helps promote the effectiveness of a vaccine by reducing the amount or frequency of the required dose, by prolonging the duration of immunological memory, or by modulating the involvement of humoral or cellular responses. This functional definition of adjuvants encompasses a very diverse group of substances whose chemical structures and mechanisms of action vary widely. Adjuvants for human or animal vaccines are typically subjected to rigorous standards of analysis including quantification of strength, purity, stability, and degradation behavior, even though they are not currently regulated in the same manner as active pharmaceutical ingredients in the US. Complicating such analysis, many adjuvants under investigation contain components that are not readily analyzed by traditional HPLC with UV detection. These include various mixtures of lipids, fatty acids, and glycosides that lack suitable UV chromophores

Amino acids

Unwanted protein aggregation is a major degradation pathway of protein therapeutics during their storage. Stabilization of protein formulations can be enhanced through the addition of specific amino acids as well as other excipients such as surfactants and sugars. Of all the possible amino acids available only a selected few are commonly used as excipients in protein therapeutic formulations and include arginine, aspartic acid, glutamic acid, glycine, histidine, lysine, proline, and methionine. They serve as antioxidants, buffers, bulking agents, and stabilizers. For example, glutamic acid and histidine can help adjust the final pH and replace organic buffers such as acetate and citrate, respectively. Methionine can be included as an antioxidant in formulations and arginine has been shown to be highly effective at suppressing aggregation in both liquid and lyophilized formulations, while alanine, glycine, proline, and serine can partially serve in this capacity as well.

Carbohydrates – cyclodextrins

Cyclodextrins are excipients that can help to solubilize various poorly soluble drugs through the formation of water-soluble drug–cyclodextrin complexes. Cyclodextrins are cyclic oligosaccharides containing six, seven, or eight (α-1,4)-linked D-glucopyranoside units, termed α-, β-, and γ-cyclodextrin, respectively. These parent cyclodextrins can have somewhat limited solubility in water, and are often chemically modified to produce cyclodextrin derivatives with greater water solubility. Formation of complexes also improve drug stability and dissolution, lead to a more rapid onset of drug action and a reduction in drug side effects.

Carbohydrates – simple sugars

Simple carbohydrates excipients are used as binders, bulking agents, and sweeteners. In protein therapeutics, like amino acids, they help control unwanted protein aggregation during storage. Typical simple carbohydrates include glucose, lactose, mannitol, mannose, sorbitol, sucrose, and trehalose.

Counterions

The biological and physicochemical properties of an API is greatly affected by its salt form. Selection of a particular counterion can be used to increase or decrease API solubility, alter dissolution rate, improve stability, decrease toxicity, reduce hygroscopicity, improve permeability, and improve drug efficacy.

Poloxamers

Poloxamers are nonionic surfactants used in pharmaceuticals and cosmetics. They are used in pharmaceutical formulations as dispersing agents, emulsifying agents, solubilizing agents, and surfactants. Poloxamers are used in cell culture media as a cellular protectant from the hydrodynamic forces and shear stress during bioprocessing.

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Polyethylene glycol

Polyethylene glycol (PEG) is used by the pharmaceutical industry as a solvent, plasticizer, surfactant, and as a vehicles in dermatological applications, suppositories, parenterals, tablets, and pills. PEG is also attached to biopharmaceutical drugs (PEGylation) to slow down their degradation, increase their duration of action, and to reduce immunogenicity. Macrogol, is the international nonproprietary name for PEG when it is used in medicine.

Polysorbates

Polysorbates are non-ionic surfactants and emulsifiers and are used in large quantities throughout the pharmaceutical, food, and cosmetic industries. In biopharmaceuticals polysorbates prevent surface adsorption and stabilizes proteins against stress-induced aggregation, such as agitation and shear. Due to the significant demand across industries polysorbates are often produced in large lots with the presence of varying limits of impurities (e.g., peroxides, carbonyls, and metals). The characterization and quantification of polysorbates is difficult because these compounds are heterogeneous mixtures with no chromophore. As a result, physical tests and testing for impurities are typically used for release criteria. While this testing is sufficient for the manufacturers to release quality material, it may not be sufficient for the end user. Because polysorbates are used in final formulations, determination of lot-to-lot variability is critical to both the pharmaceutical and biopharmaceutical industries.

Surfactants

Surfactants (surface active agents) are a diverse group of chemicals whose structures vary widely but typically contain an oil-soluble hydrophilic chain and a water soluble hydrophilic group. Surfactants can be categorized based upon their structure and include both ionic (anionic, cationic, and zwitterionic) and nonionic classes. Surfactants play a number of roles including: modulating solubility of APIs, influencing bioavailability of APIs, improving the stability of active ingredients in the dosage forms, modulating immunogenic responses of active ingredients, preventing aggregation or dissociation, helping APIs to maintain preferred polymorphic forms, maintaining the pH and/or osmolality of liquid formulations, maintaining viscosity, acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and disintegrants. Surfactants are also used to create emulsions including creams, ointments, liniments, pastes, films, and liquids.

Triton X-100

Triton X-100 (octoxynol-10) is a nonionic surfactant and detergent used to solubilize proteins and help form emulsions. It is also used as a vaccine excipient.

Title	Authors	Publication
HPLC-Charged Aerosol Detection Surfactants and Emulsifiers Applications Notebook	Acworth, I.; Fabel, S.	AN71104, 2019
Charged Aerosol Detection and Method Transfer of Compendial, Including USP, Methods	Lovejoy, K.; Acworth, I. N.; Gamache, P. H.	PO79234, 2019
Deoxycholic Acid Method Transfer from The Corona Ultra RS Charged Aerosol Detector to The Corona Veo (or Vanquish) Charged Aerosol Detector	Lovejoy, K.; Gamache, P. H.; Muellner, T.; Acworth, I. N.	AN72600, 2018
Metoprolol Impurity Testing by Charged Aerosol Detection: Method Transfer and Optimization of a USP Method	Lovejoy, K.; Gamache, P. H.; Muellner, T.; Acworth, I. N.	AN72763, 2018
Charged Aerosol Detection—Factors Affecting Uniform Analyte Response	Menz, M.; Eggart, B.; Lovejoy, L.; Acworth, I. N.; Gamache, P. H.; Steiner, F.	TN72806, 2018
Quantitation of Paclitaxel, its Degradants, and Related Substances using UHPLC with Charged Aerosol Detection	Menz, M.; Steiner, F.	AN72594, 2018
HPLC-CAD Impurity Profiling of Carbocisteine using SCX-RP Mixed-mode Chromatography	Schiling, K.; Pawellek, R.; Wahl, O.; Holzgrabe, U.	AN72706, 2018
Fatty Acid Analysis in Polysorbate 80 by UHPLC-CAD	Schilling, K.; Pawellek, R.; Lovejoy, K.; Muellner, T.; Holzgrabe, U.	PO72788, 2018
A Highly Sensitive High-Performance Liquid Chromatography-Charged Aerosol Detection Method for the Quantitative Analysis of Polysorbate 80 in Protein Solution	Long, Z.; Shen, G.; Neubauer, M.; Lovejoy, K.; Liu, L.; Liu, X.; Jin, Y.; Liu, X.	AN72398, 2017
Quantitation of APIs and Impurities in Multi-component Drugs by Ternary Gradient Reversed Phase Chromatography with Charged Aerosol Detection	Lovejoy, K.; de Pra, M.; Steiner, F.	PO72411, 2017
Advanced UHPLC Setups to Overcome Limitations of Nebulizer-Based Detectors	Paul, C.	TN70922, 2014
Metoprolol and Selected Impurities Analysis Using Hydrophilic Interaction Chromatography Method with Combined UV and Charged Aerosol Detection	Bailey, B.	AN1126, 2016
Simultaneous Determination of Tartaric Acid and Tolterodine in Tolterodine Tartrate	Chantarasukon, C.; Tukkeeree, S.; Rohrer, J.	AN70356, 2016
Quantification of Drug Metabolites in Early-Stage Drug Discovery Testing	Crafts, C.; Bailey, B.; Waraska, J.; Acworth, I.	PN70036, 2016
Enhancement of Linearity and Response in Charged Aerosol Detection	Crafts, C.; Plante, M.; Bailey, B.; Acworth, I.	PN70003, 2016
Sensitive Analysis of Underivatized Amino Acids Using UHPLC with Charged Aerosol Detection	Crafts, C.; Plante, M.; Bailey, B.; Acworth, I.	PN70038, 2016
Novel Analytical Methods to Verify Effectiveness of Cleaning Processes	Crafts, C.; Plante, M.; Bailey, B.; Acworth, I.	PN70035, 2016

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Title	Authors	Publication
Analytical Methods to Qualify and Quantify PEG and PEGylated Biopharmaceuticals	Crafts, C.; Bailey, B; Plante, M.; Acworth, I.	PN70052, 2016
Use of C30 as a General-Purpose Stationary Phase for a Broad Range of Applications	Heidorn, M.; Liu, X.; Tracy, M.; Pohl, C.	LPN2868, 2016
Gentamicin Sulfate Assay by HPLC with Charged Aerosol Detection	Li, R.; Hurum, D; Wang, J.; Rohrer, J.	AN70016, 2016
A Platform Method for Pharmaceutical Counterion Analysis by HPLC	Liu, X.; Tracy, M.; Pohl, C.	PN20948, 2016
Simultaneous Determination of Metformin and its Chloride Counterion Using Multi-Mode Liquid Chromatography with Charged Aerosol Detection	Liu, X.; Tracy, M.	AN20868, 2016
A Sensitive Method for Direct Analysis of Impurities in Apramycin and Other Aminoglycoside Antibiotics Using Charged Aerosol Detection	Long, Z.; Zhang, Q.; Jin, Y.; Bailey, B.; Acworth, I.; Mohindra, D.	PN64683, 2016
Towards Standard-Free Quantitative and Qualitative Analysis in Liquid Chromatography	Martin, M.; Heidorn, M.; Steiner, F.; Plante, M.; McLeod, F.	LPN2881, 2016
Optimizing and Monitoring Solvent Quality for UV-Vis Absorption, Fluorescence and Charged Aerosol Detectors	Neubauer, M.; Franz, H.	TN70818, 2016
Determination of Virginiamycin; Erythromycin; and Penicillin in Dried Distillers Grains with Solubles	Perati, P.; De Borba, B ; Rohrer, J.	AN70519, 2016
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Characterization and Lot-to-Lot Variability of Complex Surfactants by High Performance Liquid Chromatography and Charged Aerosol Detection	Plante, M.; Acworth, I.; Bailey, B.; Sneekes, E-J.; Steiner, F.	PN64687, 2016
Quantitation of Pluronics by High Performance Liquid Chromatography and Corona Charged Aerosol Detection	Plante, M.; Bailey, B.; Acworth, I.	PN70535, 2016
Quantitation of Surfactants in Samples by high Performance Liquid Chromatography and Corona Charged Aerosol Detection	Plante, M.; Bailey, B.; Acworth, I.	PN70539, 2016
Direct Analysis of Surfactants using HPLC with Charged Aerosol Detection with Charged Aerosol Detection	Plante, M.; Bailey, B.; Acworth, I.; Crafts, C.	PN70055, 2016
Multi-Modal Analyte Detection of Cyclodextrin and Ketoprofen Inclusion Complex Using UV and CAD on an Integrated UHPLC System	Plante, M.; Bailey, B.; Acworth, I.; Sneekes, E-J.; Steiner, F.	PN71690, 2016
Guidelines for Method Transfer and Optimization of the Corona Veo Charged Aerosol Detector	Plante, M.; Bailey, B.; Gamache, P.; Acworth, I.	PN64690, 2016
Effect of Mobile Phase Quality on Analytical Performance of Corona Charged Aerosol Detectors	Plante, M.; Bailey, B.; Kusinitz, F.; Acworth, I.	TN71390, 2016

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Title	Authors	Publication
Determination of Proteins and Carbohydrates by 2D HPLC (RPLC and HILIC) with Charged Aerosol and Ultraviolet Detection	Plante, M.; Acworth, I.; Bailey, B.; Sneekes, E-J.; Steiner, F.	PN64685, 2016
A New Approach to the Simultaneous Analysis of Underivatized Ionophoric Antibiotics using Liquid Chromatography with Charged Aerosol Detection	Plante, M.; Bailey, B.; Acworth, I.; Crafts, C.	PN70054, 2016
Analysis of Gentamicin Using a pH Stable Specialty Column for Aminoglycoside Antibiotics Separation	Sun, X.; Liu, X.	AN21438, 2016
Charged Aerosol Detection and Evaporative Light Scattering Detection—Fundamental Differences Affecting Analytical Performance	Thomas, D.; Bailey, B.; Plante, M.; Acworth, I.	PN70990, 2016
Direct Analysis of Multicomponent Adjuvants by HPLC with Charged Aerosol Detection	Thomas, D.; Acworth, I.; Bailey, B.; Plante, B.	PN70333, 2016
Monitoring Peptide PEGylation by HPLC with Charged Aerosol Detection	Thomas, D.; Acworth, I.; Meier, S.; Kaboord, B.; Yang, H.; Fisher, C.	PN72093, 2016
2D Analysis of Protein Therapeutics and Amino Acid Excipients with Combined UV and Charged Aerosol Detection	Thomas, D.; Acworth, I.; Bauder, R., Plante, M.; Kast, L.	PN71849, 2016
API and Counterions in Adderall® Using Multi-mode Liquid Chromatography with Charged Aerosol Detection	Tracy, M.; Liu, X.	AN20870, 2016
Separation of Biochemical Buffering Agents Using Multi-Mode Liquid Chromatography with Charged Aerosol Detection	Tracy, M.; Liu, X.	AN20977, 2014
Application of Charged Aerosol HPLC Detection in Biopharmaceutical Analysis	Kopaciewicz, B.; Thomas, D.; Bailey, B.: Zhang, Qi.; Plante, M.; Acworth, I.	PN71803, 2015
A Gentamicin Sulfate Assay Using HPLC-charged Aerosol Detection with an Ion-Pairing Reagent Gradient	Li, R.; Hurrum, D.; Wang, J.; Rohrer, J.	PO70136, 2012
Analysis of Silicone Oils by High Performance Liquid Chromatography and Corona Charged Aerosol Detection	Plante, M.; Bailey, B.; Acworth, I.	PN70538, 2016
Charged Aerosol Detection Applications Guide		TG70712, 2013
Analysis of Cationic Surfactants on the Acclaim Surfactant Plus HPLC Column	Foley, D.; Faulkner, W.	AN20574, 2012
Acclaim™ Surfactant Column Product Manual	Unknown	PN065530-01, 2013
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Semiquantitative Analysis for High-Throughput Screening of Compound Libraries	Crafts, C.; Plante, M.; Malek, G.; Neely, M.; Acworth, I.	LPN2956, 2011

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Title	Authors	Publication
Simple, Sensitive, and Semiquantitative Analytical Approach for Cleaning Validiation Studies	Hvizd, M.; Crafts, C.; Bailey, B.; Plante, M.; Acworth, I.	LPN2955, 2011
Simple Separation and Detection Techniques for the Analysis of Carbohydrates	Hvizd, M.; Bailey, B.; Crafts, C.; Plante, M.; Acworth, I.	LPN2954, 2011
Use of Charged Aerosol Detection as an Orthogonal Quantification Technique for Drug Metabolites in Safety Testing (MIST)	Malek, G.; Crafts, C.; Plante, M.; Neely, M.; Bailey, B.	LPN2953, 2011
Evaluation of Methods for the Characterization and Quantification of Polysorbates and Impurities Along with Other Surfactants and Emulsifiers Used in the Food and Pharmaceutical Industries	Plante, M.; Fitchett, A.; Hvizd, M.	LPN2991, 2011
Using Charged Aerosol Detection as a Universal Approach to Analyze Pharmaceutical Salts Including Inorganic and Organic Counterions	Crafts, C.; Plante, M.; Bailey, B.; Gamache, P.; Waraska, J.; Acworth, I.; Srinvasan, K.	LPN2611, 2010
Advances in Universal Detection	Bailey, B.; Plante, M.; Crafts, C.; Acworth, I.	LPN2562, 2010
Improving the Quantitation of Unknown Impurity Analysis Using Dual-Gradient HPLC with Charged Aerosol Detection	Crafts, C.; Bailey, B.; Plante, M.; Waraska, J.; Acworth, I.	LPN2666, 2010
Using Charged Aerosol Detection as a Universal Approach to Analyze Pharmaceutical Salts Including Inorganic and Organic Counterions	Crafts, C.; Plante, M.; Bailey, B.; Gamache, P.; Waraska, J.; Acworth, I.; Srinvasan, K.	LPN2611, 2010
New Approaches for Simultaneous API and Counterion Analysis Using Charged Aerosol Detection	Crafts, C.; Plante, M.; Bailey, B.; Gamache, P.; Waraska, J.; Acworth, I.; Srinvasan, K.	LPN2610, 2010

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Title	Authors	Publication
Development of a Rapid and Reliable Analytical Method for Screening Poloxamer 188 for Use in Cell Culture Process.	Bareford, L.; Peng, H.; Ali, A.; Kolwyck, D.; Dickens, J.	*Biotechnol. Prog.* **2019**, *35, e2792.*
Mechanism for the Reduced Dissolution of Ritonavir Tablets by Sodium Lauryl Sulfate.	Guo, Y.; Wang, C.; Dun, J.; Du, L.; Hawley, M.; Sun. C. C.	*J. Pharm. Sci.* **2019**, *108, 516–524.*
On-line Coupling of Hydrophobic Interaction Column with Reverse Phase Column-Charged Aerosol Detector/Mass Spectrometer to Characterize Polysorbates in Therapeutic Protein Formulations.	He, Y.; Brown, P.; Bailey Piatchek, M. R.; Carroll, J. A.; Jones, M. T.	*J. Chromatogr. A* **2019**, *1586, 72–81.*
Microwave-Assisted Synthesis and Characterization of Stearic Acid Sucrose Ester: A Bio-Based Surfactant.	Kondamudi, N.; MsDougal, O. M.	*J. Surfact. Deterg.* **2019**, *22, 721–729.*
Factors Influencing Polysorbate's Sensitivity Against Enzymatic Hydrolysis and Oxidative Degradation.	Kranz, W.; Wuchner, K.; Corradini, E.; Berger, M.; Hawe, A.	*J. Pharm. Sci.* **2019**, *108, 2022–2032.*
Quantitative Structure-Property Relationship Modeling of Polar Analytes Lacking UV Chromophores to Charged Aerosol Detector Response.	Schilling, K.; Krmar, J.; Maljurić, N.; Pawellek, R.; Protić, A.; Holzgrabe, U.	*Anal. Bioanal. Chem.* **2019**, *411, 2945–2959.*
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Simultaneous Determination of Anionic, Amphoteric and Cationic Surfactants Mixtures in Surface Water.	Paun, I.; Iancu, V. I.; Cruceru, L.; Niculescu, M.; Chiriac, F. L.	*Ecolib.* **2018**
Influence of Charged Aerosol Detector Instrument Settings on The Ultra-High-Performance Liquid Chromatography Analysis of Fatty Acids in Polysorbate 80.	Schilling, K., Pawellek, R., Lovejoy, K., Muellner, T., Holzgrabe, U.	*J. Chromatogr. A* **2018**, *1576, 58–66.*
PEG Quantitation Using Reversed-Phase High-Performance Liquid Chromatography and Charged Aerosol Detection.	Smith, M. C.; Clogston, J. D.	*Meth. Mol. Biol.* **2018**, *1682, 49–55.*
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Title	Authors	Publication
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Pilot Scale Production of a Phospholipid-Enriched Dairy Ingredient by Means of an Optimised Integrated Process Employing Enzymatic Hydrolysis, Ultrafiltration and Super-Critical Fluid Extraction.	Barry, K. M.; Dinan, T. G.; Kelly, P. M.	*Innov. Food Sci. Emerg. Tech.* **2017**, *41, 301–306.*
Analytical Stability-Indicating Methods for Alogliptin in Tablets by LC-CAD and LC-UV.	Bertol, C. D.; Friedrich, M. T.; Carlos, G.; Froehlich, P. E.	*J. AOAC Int.* **2017**, *100, 400–405.*
Determination of Quaternary Ammonium Muscle Relaxants with Their Impurities in Pharmaceutical Preparations by LC-CAD.	Blazewicz, A.; Poplawska, M.; Warowna-Grzeskiewicz, M.; Sarna, K.; Fijalek, Z.	*Charged Aerosol Detection for Liquid Chromatography and Related Separation Techniques; Gamache, P. H., Ed.; Wiley: New York,* **2017**; *p 425.*
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Impurity Control in Topiramate with High Performance Liquid Chromatography.	Ilko, D.; Neugebauer, R. C.; Brossard, S.; Almeling, S.; Turk, M.; Holzgrabe, S.	*Charged Aerosol Detection for Liquid Chromatography and Related Separation Techniques; Gamache, P. H., Ed.; Wiley: New York,* **2017**; *p 379.*
Applying Charged Aerosol Detection to Aminoglycosides: Development and Validation of an RP-HPLC Method for Gentamicin and Netilimicin.	Joseph, A.; Rustum, A.	*Charged Aerosol Detection for Liquid Chromatography and Related Separation Techniques; Gamache, P. H., Ed.; Wiley: New York,* **2017**; *p 393.*
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Analytical Characterization of an Oil-in-Water Adjuvant Emulsion.	Sun., J.; Remmele, R. L. Jr.; Sanyal, G.	*AAPS Pharm. Sci. Tec.* **2017**, *18, 1595–1604.*
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Impurity Profiling of N,N'-Ethylenebis-L-Lysteine Diethyl Ester (Bicisate).	Wahl, O.; Cleynhens, J.; Verbruggen, A. M.; Holzgrabe, U.	*J. Pharm. Biomed. Anal.* **2017**, *150, 132–136.*
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Direct Determination of Amino Acids by Hydrophilic Interaction Liquid Chromatography with Charged Aerosol Detection.	Socia, A.; Foley, J. P.	*J. Chromatogr. A* **2016**, *1446, 41–49.*
Amino Acid Analysis for Pharmacopoeial Purposes.	Wahl, O.; Holzgrabe, U.	*Talanta* **2016**, *154, 150–163.*
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Sensitive and Direct Determination of Lithium by Mixed-Mode Chromatography and Charged Aerosol Detection.	Dai, L.; Wigman, L.; Zhang, K.	*J. Chromatogr. A* **2015**, *1408, 87–92.*
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Quantitative Analysis of PEG-Functionalized Colloidal Gold Nanoparticles Using Charged Aerosol Detection.	Smith, M. C.; Crist, R. M.; Clogston, J. D.; McNeil, S. E.	*Anal. Bioanal. Chem.* **2015**, *407, 3705–3716.*
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A Comparative Study on the Analytical Performance of a Charged Aerosol Detector and an Ultraviolet Detector for the RP-LC Analysis of Dabigatran Etexilate in Capsules.	Bernardi, R. M.; D'Avila, F. B.; Todeschini, V.; Froehlich, P. E.; Bergold, A. M.	*Anal. Meth.* **2013**, *5, 4777–4784.*
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