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- Optimized impurity analysis methods
- Guide to optimize your methods
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- Unique tools for impurity analysis
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Optimized impurity analysis methods

Many established impurity tests are routinely performed with HPLC with optical absorption detection, here we demonstrate some of the many examples of established compendial methods with increased performance, and how they can be optimized to make the most of your analysis time. **Click on note titles to jump to page.**

Forced-degradation evaluation of erythromycin by HPLC and single quadrupole mass spectrometry

Mauro De Pra, Stephan Meding, Thermo Fisher Scientific, Germering, Germany

Keywords
Vanquish Core, ISQ EC, ISQ EM, antibiotics, pharmaceutical analysis, stability studies

Introduction

Mass spectrometric (MS) detection can address the limitations of UV-based LC purity analysis in forced degradation studies. Since the molecular mass of the expected synthesis-related impurities is known, the hyphenation of mass detection with LC enables putative identification of peaks without the need for standards. Described here is a method developed using the European Pharmacopeia SST CRS-1 standard. With the aim of keeping HPLC method development effort to a minimum, only one column and few elution conditions were tested.

- Thermo Scientific™ Vanquish™ Core HPLC system
- Thermo Scientific™ ISQ™ EM Single Quadrupole mass spectrometer
- Thermo Scientific™ Acclaim™ PolarAdvantage II analytical column

Goal

Develop a simple, stability-indicating LC-MS method for erythromycin. Compare the impurity profiles of an erythromycin reference standard with stressed analyte.

Conclusions

A fit-for-purpose LC-MS method to assess the purity profile of erythromycin stressed samples was developed with low effort. Mass detection enabled assessment of the relative impurity content in spite of erythromycin A co-eluting with two impurities. Injection of less than 3 µg sample was sufficient to obtain satisfactory sensitivity. The amount injected is more than 100 times lower than that recommended by the EP method.

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Identity confirmation and accurate quantitation of a genotoxic impurity in an active pharmaceutical ingredient by UHPLC-UV coupled to a single quadrupole mass detector

Sylvia Grosse, Mauro De Pra, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords
Genotoxic impurities, methyl-p-toluenesulfonate, aprepitant, ISQ EM, single quadrupole, mass detection, UV detection, Autospray

Introduction

The aim of this study was to develop a method for monitoring and quantifying methyl-ptoluenesulfonate along with other related impurities in a drug substance. The API chosen in this study is aprepitant. Aprepitant is an antiemetic administered for the prevention of nausea and vomiting during chemotherapy. Contamination of aprepitant by genotoxic methyl-p-toluenesulfonate may occur, since p-toluenesulfonic acid and methanol are used in different steps of the synthesis.

- Thermo Scientific™ ISQ™ EM mass spectrometer
- Thermo Scientific™ Vanquish™ Flex UHPLC system with Diode Array Detector
- Thermo Scientific™ Acclaim™ PA II analytical column

Goal

Confirm the identity of related impurities and a genotoxic impurity in a drug substance by single quadrupole mass detector. Accurately quantify the genotoxic impurity by UV detection.

Conclusions

Mass detection delivers easy and reliable peak identity confirmation. Sensitive UV detection provides quantitation of a genotoxic impurity at low ng/mL level. Easy and user-friendly adjustment of the ion source parameter settings with Autospray.

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Global round robin test of thiopental EP method performance on identical HPLC systems

Sylvia Grosse, Katherine Lovejoy, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords

Reproducibility, precision, European Pharmacopoeia, system suitability test, UV-Vis, thiopental, variability, small molecule pharmaceutical

Introduction

In this technical note, we present the results of a global round robin test designed to evaluate the system-to-system reproducibility. Multiple HPLC instruments of the same model were used to analyze thiopental and its impurities as described by the related substances method in the current monograph published by the European Pharmacopoeia (EP). For that purpose, eight labs and seven operators in four countries on three continents were equipped with identical HPLC instruments but different pumping technologies and UV detector types and were asked to perform the exact same analysis.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector or Variable Wavelength Detector
- Thermo Scientific™ Hypersil GOLD™ analytical column

Goal

Evaluate system-to-system variability, while controlling for different operators, column lots, and solvent grades. Present intra- and inter-laboratory precision data for retention time, peak areas, and relative quantification.

Conclusions

The presented results show that Thermo Scientific™ Vanquish™ Core HPLC systems have excellent system-to system reproducibility when the sample preparation, eluent preparation, and LC column are identical. Users can rely on the fact that the performance of multiple Vanquish Core HPLC systems will be highly predictable and robust for routine methods in quality control labs when other variables are controlled.

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Setup and transfer of a gradient HILIC method for the impurity analysis of temozolomide

Maria Grübner, Thermo Fisher Scientific, Germering, Germany

Keywords
HPLC method transfer, Vanquish Core HPLC system, Agilent 1260 Infinity LC system, temozolomide, HILIC, Ph. Eur., USP

Introduction

The chromatographic method for the impurity analysis of temozolomide provided by the monographs of the European and the United States Pharmacopeia (Ph. Eur. and USP) specifies a C18 stationary phase and a highly aqueous mobile phase with the ion-pairing reagent hexanesulfonate to separate the active pharmaceutical ingredient (API) and four related impurities. In the current work, an alternative HILIC method was set up and was transferred from an Agilent 1260 Infinity LC (1260 Infinity) system to a Vanquish Core HPLC system.

- Thermo Scientific™ Vanquish™ Core HPLC system with Variable Wavelength Detector
- Thermo Scientific™ Syncronis™ HILIC analytical column

Goal

Develop an analytical HILIC method and transfer it from an Agilent 1260 Infinity LC system to the Vanquish Core HPLC system.

Conclusions

A fast and reproducible gradient HILIC method was set up for the impurity analysis of the hydrophilic temozolomide. Straightforward transfer of the method from an Agilent™ 1260 Infinity™ LC system to a Thermo Scientific™ Vanquish™ Core HPLC system was demonstrated. Equivalent chromatographic results were obtained.

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Easy transfer of an EP method for chlorhexidine impurity analysis from a Shimadzu Nexera-i system to a Vanquish Core HPLC system

Maria Grübner, Thermo Fisher Scientific, Germering, Germany

Keywords
HPLC method transfer, Vanquish Core HPLC system, Shimadzu Nexera-i, Chromeleon CDS, chlorhexidine, European Pharmacopoeia

Introduction

In the following, the HPLC method for impurity analysis of chlorhexidine digluconate given by the European Pharmacopoeia (EP) monograph is transferred from a Shimadzu Nexera-i system to a Vanquish Core Quaternary HPLC system. Chlorhexidine is a common antiseptic and disinfectant, listed on the World Health Organization's (WHO) Model List of Essential Medicines. It is available as an over-the-counter drug and is widely used in dental medicine and hygiene, for example, in mouthwashes and for skin disinfection purposes.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Hypersil GOLD™ analytical column

Goal

To showcase the transfer of analytical HPLC methods from a Shimadzu Nexera-i system to the Vanquish Core HPLC system and highlight the easy-to-use gradient delay volume (GDV) adjustment features of the Vanquish Core HPLC system.

Conclusions

Straightforward transfer of an EP monograph HPLC method from a Shimadzu™ Nexera-i™ system to a Thermo Scientific™ Vanquish™ Core Quaternary HPLC system is demonstrated. Advanced hardware features of the Vanquish Core HPLC system enable flexible adjustments of the overall system gradient delay volume to facilitate compliant fine-tuning during the transfer. Equivalent chromatographic results are obtained with the originating and receiving instrument, but improved system precision is provided by the Vanquish Core HPLC system.

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Overcoming strong solvent effects during method transfer of a compendial method for the analysis of hesperidin

Ruiping Chai[1], Tibor Muellner[2], Jianming Cao[3], Yan Jin[3], Frank Steiner[2]
[1]Thermo Fisher Scientific, Beijing, China, [2]Thermo Fisher Scientific, Germering, Germany, [3]Thermo Fisher Scientific, Shanghai, China

Keywords
Vanquish Core HPLC system, strong solvent loop, compendial methods, strong solvent effect, HPLC method transfer, Chinese Pharmacopeia, traditional Chinese medicine, Xingsu Zhike Koufuye

Introduction

Using a compendial method for the determination of hesperidin as described in the 2020 Chinese Pharmacopeia, we demonstrate the occurrence of strong solvent effects when the method is run unaltered on a Vanquish Core instrument. We show the use of custom injection programs as a software-based mitigation strategy, as well as the use of a strong solvent loop as a hardware-based solution to mitigate the negative affect of strong solvent injections and improve the peak shape.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Acclaim™ C18 analytical column

Goal

To demonstrate the use of the Thermo Scientific™ Vanquish™ Core HPLC System equipped with a strong solvent loop to mitigate strong sample solvent effects occurring in a compendial method.

Conclusions

A compendial method for the analysis of hesperidin was transferred to the Vanquish Core HPLC system. Different approaches to handling strong solvent effects are demonstrated to be successful. A simple and compliant way to mitigate strong sample solvent effects is demonstrated.

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Straightforward implementation of a compendial LC method for metolazone impurity analysis with the Vanquish Core HPLC system

Maria Grübner, Thermo Fisher Scientific, Germering, Germany

Keywords
HPLC, Vanquish Core HPLC system, metolazone, European Pharmacopoeia, routine analysis, pharma

Introduction

In the current application brief, seamless implementation of a liquid chromatographic analytical method published by the European Pharmacopoeia (Ph. Eur.) is demonstrated using the Vanquish Core HPLC system. The API metolazone is a diuretic drug, which is used in the treatment of high blood pressure. The method published in the monograph serves to separate the API and five known impurities to allow accurate quantitation.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Hypersil™ ODS C18 analytical column

Goal

Highlight the reliability of the Thermo Scientific™ Vanquish™ Core HPLC system in routine LC analysis.

Conclusions

Reliable and highly reproducible chromatographic results were obtained when implementing the liquid chromatography (LC)-based impurity method from the Ph. Eur. monograph of metolazone.

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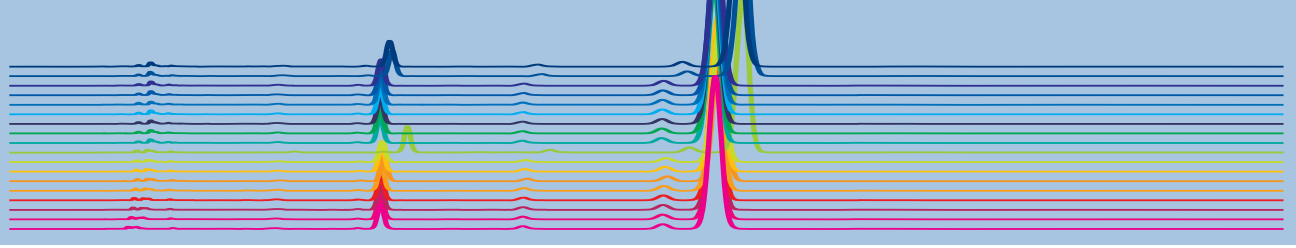

Long-term robustness of thiopental Ph. Eur. method performance on modern HPLC instrumentation

Markus M. Martin, Sylvia Grosse, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords

Long-term robustness, reproducibility, European Pharmacopoeia, thiopental, variability, small molecule pharmaceutical, Vanquish Core HPLC system

Introduction

In the present technical note, we investigate the long-term precision of an established routine analysis for thiopental and its by-products as described by the European Pharmacopoeia (EP) . For that purpose, multiple sequences of thiopental analyses were repeated by one fixed operator with one fixed assigned Vanquish Core HPLC system and a total time window ranging over 3.5 months. In addition to this multi-sequence approach, we also looked at the robustness of this method when performed over a large number of injections covering a total run time of more than three consecutive days.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Hypersil GOLD™ analytical column

Goal

Evaluate intra-system variability of retention times and peak areas on a larger time scale of several months. Demonstrate the superiority of the pump proportioning performance compared to the original Ph. Eur. method by a 3-day sequence of 170 sequential injections.

Conclusions

The results of a long-term robustness study run on a Thermo Scientific™ Vanquish™ Core Quaternary HPLC system show excellent intra-sequence reproducibility and merely minor variations of retention times and peak area over a timespan of more than 3 months. The biggest impact factors are the mobile phase preparation and shelf life, while the Vanquish Core system robustness excels all regulatory requirements with a retention time precision of 0.07% over 170 injections when the mobile phase is prepared by blending the pure solvents via the low-pressure gradient pump.

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Analysis of cefprozil and related impurities by reversed-phase liquid chromatography with UV detection

Soo Hyun Park, Sylvia Grosse, Mauro De Pra, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords
Cefprozil, cefprozil related impurity, Ph. Eur. method, HPLC, Vanquish Core, Hypersil GOLD aQ, European Pharmacopeia, impurity, system suitability

Introduction

In this application note amethod for the analysis of cefprozil related impurities is performed using a Vanquish Core high performance liquid chromatography (HPLC) system. The method is based on the cefprozil monohydrate European Pharmacopoeia (Ph. Eur.) monograph and is suitable for impurity analysis for batch-release or stability evaluation.

- Thermo Scientific™ Vanquish™ Core HPLC system
- Thermo Scientific™ Hypersil GOLD™ column

Goal

To demonstrate the European Pharmacopoeia based analysis of impurities in cefprozil with the new Vanquish Core HPLC system.

Conclusions

The quantification of cefprozil-related impurities based on the Ph. Eur. method was successfully demonstrated. The Vanquish Core HPLC system delivered high precision in retention time and area. The Hypersil GOLD aQ column provided sufficient separation of impurity F and cefprozil Z-isomer, outperforming the criteria for system suitability.

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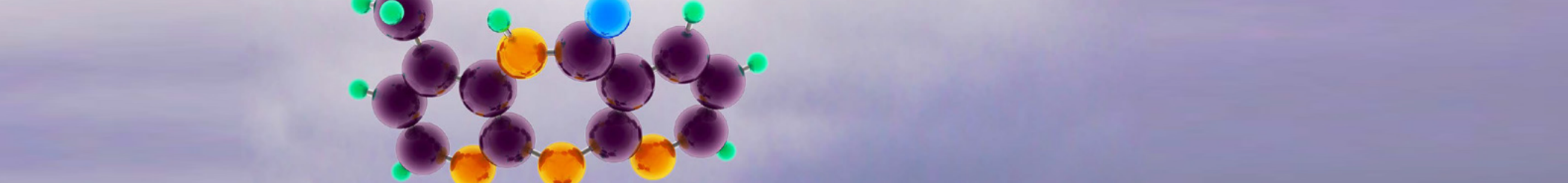

Simultaneous quantification of nevirapine and low-level impurities

Maria Grübner, Frank Steiner, Holger Franz, Thermo Fisher Scientific, Germering, Germany

Keywords
Thermo Scientific Vanquish DAD FG, nevirapine, impurity profiling, linear range

Introduction

For impurity profiling, the United States Pharmacopoeia (USP)5 provides an HPLC method with UV detection that was transferred into an optimized UHPLC method with ballistic. This method was used in the current study to demonstrate the capabilities of the new Thermo Scientific Vanquish DAD FG to quantify both the API nevirapine and its impurities A, B, and C in a single run.

- Thermo Scientific™ Vanquish™ Horizon UHPLC system with Diode Array Detector
- Thermo Scientific™ Syncronis™ C18 analytical column

Goal

To demonstrate the wide dynamic range of the new Thermo Scientific Vanquish DAD FG and how it facilitates the quantification of compounds of very different concentrations.

Conclusions

The Vanquish DAD FG combines a very wide linear range with the best noise performance, enabling for the simultaneous quantification of APIs and impurities within a single run. Excellent quantitative results were obtained for the API nevirapine and its impurities with an optimized UHPLC method with deviations from expected amounts of less than 2% for the API and 6–21% for impurities under the approximated assumption of equivalent responses. Impurity quantification was possible down to 0.012% relative area if the linear detection range is fully exploited.

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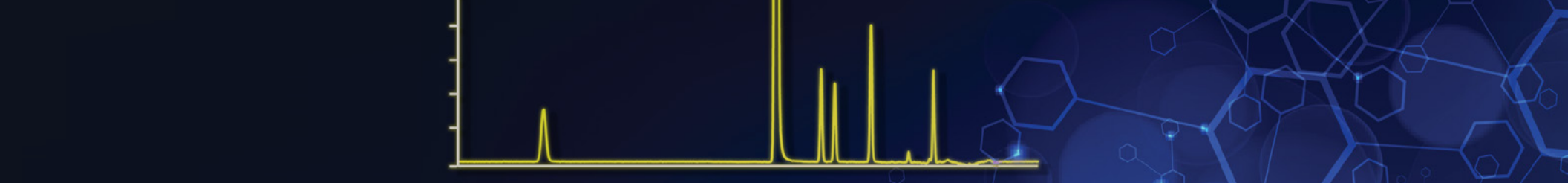
Guide to optimizing your methods

It is crucial that existing methods can be adapted to take advantage of the improvements in instrumentation and associated consumables. Laboratories need the ability to transfer from outdated legacy instruments to replacements offering enhanced analytical speed and detection sensitivity. It is also common for laboratories to transfer methods between different instrument types, including those from different vendors. Method transfer is complex and relies on robust method development. Adaptable instruments, able to accommodate for differences between systems, help to simplify the process. **Click on note titles to jump to page.**



An instrument parameter guide for successful (U)HPLC method transfer

Carsten Paul, Maria Grübner, Michael Heidorn, Matthias Krajewski, Sabrina Patzelt, Thomas Piecha, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords
UHPLC, HPLC, USP , gradient delay volume, column thermostatting, extra-column volume, detector settings

Introduction

The transfer of analytical procedures in liquid chromatography (LC) is a regular task in many laboratories. This challenge can be categorized into the following common scenarios:

- Acceleration of methods, e.g. from HPLC to UHPLC methods
- Method transfer to identical equipment, e.g. in another laboratory
- Method transfer to a non-identical instrument, e.g. to a recently purchased system

Goal

Explain in detail the instrumental parameters HPLC users need to consider during transfer of an analytical HPLC method between different instruments.

Conclusions

Transferring HPLC methods depends on several different factors that often make this task very difficult for chromatographers. For instance, non-matching retention times can be caused by multiple facors described. A loss of resolution also can be caused by multiple reasons.

These two criteria illustrate how complex method transfer can be even when only the instrumental parameters are considered—aspects related to the column used, eluents, or other consumables are not even taken into account. The guidance given here allows for the root cause analysis of deviation observed.

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Doubling the throughput of long chromatographic methods by using a novel Dual LC workflow

Sylvia Grosse[1], Shaun Quinn[2], Mauro De Pra[1], Frank Steiner[1]
[1]Thermo Fisher Scientific, Germering, Germany, [2]Thermo Fisher Scientific, Altrincham, Great Britain

Keywords
Vanquish Duo UHPLC system for Dual LC, ezetimibe, simvastatin, pharmaceutical, related impurity analysis

Introduction

In this work, we introduce a novel Dual LC workflow, which provides a unique concept by using two separated flow paths in one system. The Dual LC workflow enables the simultaneous analysis of two samples by the same instrument, in practice doubling the laboratory throughput within the footprint of one instrument. The Vanquish Flex Duo system for Dual LC consists of a Dual Pump F with two individual pumping units, a Dual Split Autosampler FT with two separate injection valves and sample loops, one—or optionally two—Column Compartments H, and two detectors.

- Thermo Scientific™ Vanquish™ Flex Duo system for Dual LC
- Thermo Scientific™ Hypersil GOLD™ PFP analytical column

Goal

The Vanquish Flex Duo system for Dual LC was used for the analysis of a stressed drug mixture of ezetimibe and simvastatin. It enabled the simultaneous analysis of two samples, doubling the throughput of the stability-indicating method.

Conclusions

The Dual LC capabilities increased the number of analyses run on one instrument from 19 to 38 per day for this method with 75 minutes total run time. The Vanquish Flex Duo system for Dual LC duplicates the analysis capacity per bench space in the lab. Chromatographic results of both flow paths of the Vanquish Flex Duo system for Dual LC exhibit very good consistency both in relative retention time and relative peak area.

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Simultaneous high-performance and ultra-high-performance liquid chromatographic analysis of acetaminophen impurities using a single instrument

Maria Grübner, Carsten Paul, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords
Vanquish Flex Duo UHPLC system for Dual LC, Vanquish Flex Dual Pump UHPLC, Vanquish Flex Dual Split Sampler, acetaminophen

Introduction

To increase throughput and generate more results, there is a growing need for faster methods as well as for additional analytical instrumentation. Here, the left chromatographic channel of the novel Vanquish Flex Duo system for Dual LC was configured with HPLC common system volumes and was run with a 4.6 mm i.d. column with 3 µm particles for the analysis of acetaminophen API and its impurities derived from a USP assay. System volumes were reduced at the right channel and the respective UHPLC counterpart method, which was created by the Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) UHPLC speed-up tool, was run in parallel with a 2.1 mm i.d. column with 1.9 µm particles.

- Thermo Scientific™ Vanquish™ Flex Duo UHPLC system for Dual LC
- Thermo Scientific™ Hypersil GOLD™ C8 analytical column

Goal

To demonstrate the capabilities of the Thermo Scientific™ Vanquish™ Flex Duo UHPLC system for Dual LC to run independent HPLC and UHPLC methods simultaneously using one instrument.

Conclusions

The Vanquish Flex Duo system for Dual LC provides the opportunity to have one HPLC and one UHPLC channel in a single system stack, both working independently from each other. Speed-up of legacy HPLC methods to fast UHPLC methods can be easily conducted at the same workstation. Both channels can also be used independently for separate analyses. In the current study, a 2.5-fold throughput increase and savings of up to 80% mobile phase and 60% cycle time were achieved by speeding up a HPLC method to UHPLC conditions.

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Improving the quantitation of unknown impurity analysis using dual gradient HPLC with charged aerosol detection

Thermo Fisher Scientific

Keywords
HPLC, RSLC, charged aerosol detection, impurity analysis, pharmaceutical

Introduction

Interest in metabolite or trace impurity analysis in pharmaceutical industries is intensifying due to concerns with mass balance studies, regulatory commitments in reporting API impurities, metabolite in safety testing (MIST), and cleaning validation of manufacturing equipment. This work illustrates the application of a Thermo Scientific™ UltiMate™ 3000 Dual Gradient HPLC system combined with the inverse gradient capillary kit for the low level quantification of a group of compounds ranging in diverse chemical structure and properties, UV absorbance, HPLC retention and application in the pharmaceutical industry is presented.

- Thermo Scientific™ Dionex™ UltiMate™ 3000 Dual Gradient Rapid Separation system
- Thermo Scientific™ Acclaim™ RSLC 120 C18 analytical column

Goal

To evaluate Charged Aerosol Detection (CAD) and inverse gradient capability for universal response compared to traditional UV detection for a diverse set of compounds.

Conclusions

The use of charged aerosol detection offers increased sensitivity in a more global mass sensitive approach. The LOD (S/N >3) of the compounds used in this study was estimated between 1 to 5 ng on column, while the LOQ (S/N >10) ranged from 6 to 11 ng on column for these test compounds. The application of the inverse gradient with the UltiMate 3000 system overcomes nebulization efficiency issues and allows for quantification of nonvolatile components at trace levels without the need.

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Method validation based on ICH guidelines of a USP assay method of acetaminophen

Sylvia Grosse[1], Shaun Quinn[2], Mauro De Pra[1], Frank Steiner[1]
[1]Thermo Fisher Scientific, Germering, Germany, [2]Thermo Fisher Scientific, Altrincham, Great Britain

Keywords
Pharmacopoeia methods, analytical procedure, acetaminophen, assay method, HPLC, high-performance liquid chromatography, Vanquish Core, Chromeleon, eWorkflow, extension pack

Introduction

In this application note, the United States Pharmacopeia (USP) assay method of acetaminophen is re-validated by using Chromeleon eWorkflows with integrated data evaluation and reporting. Also shown are the advantages of such an approach, including simple and quick implementation, and the resulting time savings.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Hypersil GOLD™ C8 analytical column

Goal

Demonstrate the ease of implementation and processing of a full method validation with Chromeleon CDS using eWorkflow procedures based on the ICH guidelines.

Conclusions

Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) provides eWorkflow™ procedures for method validation based on International Council for Harmonisation (ICH) guidelines. Chromeleon eWorkflows are designed to deliver productivity and efficiency gains for method validation by significantly shortening data processing and reporting times, reduces susceptibility to errors, allows a quick and easy implementation of a full method validation with automated sequence generation, data evaluation, and reporting, reduces the time and effort to validate methods transferred to a new HPLC instrument, and is fully regulatory compliant.

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Complete workflow for determining the content of nevirapine and related impurities

Sylvia Grosse, Mauro De Pra, Frank Steiner, Thermo Fisher Scientific, Germering, Germany

Keywords

Nevirapine, Vanquish Core, Chromeleon, SST, system suitability test, Intelligent Run Control, IRC, impurity, assay, batch analysis

Introduction

This technical note describes a comprehensive data analysis of a combined assay and impurity method for nevirapine, an antiretroviral drug used in HIV/AIDS therapy. Using Thermo Scientific™ Chromeleon CDS software Intelligent Run Control (IRC) system suitability samples are automatically assessed before the analysis either continues, repeats the SSTs or aborts based upon user defined variables. Furthermore, an eWorkflow template is provided that contains a sequence as well as processing methods and report templates that can be easily adapted to the batch analysis of other APIs.

- Thermo Scientific™ Vanquish™ Core HPLC system with Diode Array Detector
- Thermo Scientific™ Acclaim™ PA II analytical column

Goal

Guidance on generating an intelligent, automated workflow for batch-release analysis of an active pharmaceutical ingredient.

Conclusions

Intelligent run control in Chromeleon CDS enables automated monitoring of SST criteria and method performance to avoid unnecessary measurements if criteria fail. Automated data processing and reporting allows for a quick, reliable data evaluation and documentation, as it is required in the pharmaceutical regulated environment.

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Dedicated nitrosamine solutions

Nitrosamine impurity analysis requires robust and sensitive analytical methods to ensure confidence in the obtained results. The wide Thermo Scientific portfolio is proven to be excellent for nitrosamine analysis, ensuring your exploratory and routine methods are performed as accurately and reliably as possible while maintaining requirements from regulatory bodies worldwide. **Click on note titles to jump to page.**

HRAM LC-MS method for the determination of nitrosamine impurities in drugs

Hao Yang, Thermo Fisher Scientific, San Jose, CA, US; Jon Bardsley, Thermo Fisher Scientific, Hemel Hempstead, UK; Min Du, Thermo Fisher Scientific, Boston, MA, US; Olaf Scheibner, Thermo Fisher Scientific, Dreieich, Germany

Keywords
Nitrosamines, NDMA, APCI, high resolution accurate mass, mass spectrometry, Orbitrap Exploris 120, Chromatography Data System, compliance-ready, generic drugs, impurities, genotoxic impurities, ranitidine, excipient, tSIM, tMS

Introduction

This application highlights a newly developed and validated high resolution accurate mass LC-MS method to detect and quantify nine nitrosamines in Ranitidine drug product within a single analytical run meeting FDA LOQ requirements of 30 ppb.

- Thermo Scientific™ Vanquish™ Horizon UHPLC system
- Thermo Scientific™ Orbitrap Exploris 120™ mass spectrometer
- Thermo Scientific™ Acclaim Polar Advantage II™, 100 × 2.1 mm, 2.2 µm

Goal

To demonstrate fast, highly sensitive quantitation of nine nitrosamines with a Thermo Scientific™ Orbitrap Exploris™ 120 mass spectrometer, and the use of the LC-MS method to measure nitrosamine impurities in commercially available ranitidine drug substances and products.

Conclusions

Exploris 120 system, the resultant method can provide reliable and confident quantitation of nine nitrosamine impurities to meet the September 2020 US FDA regulatory acceptance limits.

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APPLICATION NOTE 10753

GAS CHROMATOGRAPHY

A validated method for the rapid determination of fifteen nitrosamines in metformin drug substance

Dujuan Lu, Danny Hower – SGS Fairfield, USA
Aaron Lamb, Dominic Roberts, Cristian Cojocariu, Thermo Fisher Scientific, UK

Keywords
Metformin, nitrosamines, pharma, QC, GMP, pharmaceutical impurities, GC, high resolution mass spectrometry, HRMS, Orbitrap Exploris

Introduction

In this application note a validated analytical method using GC Orbitrap technology was developed for the selective quantification of fifteen nitrosamine impurities in metformin drug substance at ultra-trace levels.

- Thermo Scientific™ Trace™ 1310 GC system
- Thermo Scientific™ Orbitrap Exploris™ GC Mass Spectrometer
- Thermo Scientific™ TraceGOLD™ TG-1701MS™ GC Column

Goal

The purpose of this study was to develop a validated workflow for the determination of fifteen nitrosamines in metformin drug substance and to assess the quantitative performance versus ICH guidelines and FDA LOQ of 30 ppb.

Conclusions

All the methods are consistent for the determination of NDMA, while for NDEA the use of GC-MS/MS offers higher sensitivity and more accurate quantitative results.

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Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products

Hao Yang[1], Edmund Moy[1], Michael Volny[1], Claudia Martins[1], Min Du[2], Wael Elmasri[3], Tanya Tadey[4]
[1]Thermo Fisher Scientific, San Jose, CA; [2]Thermo Fisher Scientific, Boston, MA; [3]Thermo Fisher Scientific, Greenville, NC; [4]Thermo Fisher Scientific, Princeton, NJ

Keywords
Nitrosamines, nitrosamines in drugs, NDMA, APCI, HESI, nominal mass, mass spectrometry, Chromatography Data System, compliance-ready, generic drugs, nitrosamine impurities, genotoxic impurities, metformin, selected reaction monitoring, SRM

Introduction

Here, we describe a highly sensitive and robust LC-SRM-MS method using the Thermo Scientific™ Vanquish™ Horizon UHPLC system coupled to a Thermo Scientific™ TSQ Quantis™ triple quadrupole mass spectrometer to detect and quantify 10 nitrosamines in metformin drug products. The method was run in both HESI and APCI mode, with the quantitation limit for all nitrosamines below 10 ppb using HESI, or 5 ppb using APCI in both neat solution and metformin drug products. We also conducted a 1,000 sample injection test to demonstrate method reproducibility and robustness that are essential for routine screening of nitrosamines in drug products.

- Thermo Scientific™ Vanquish™ Horizon UHPLC system
- Thermo Scientific™ TSQ Quantis™ triple quadrupole mass spectrometer
- Thermo Scientific™ Hypersil GOLD™ Phenyl analytical column

Goal

To demonstrate robust and sensitive quantitation of 10 nitrosamines with a Thermo Scientific™ TSQ Quantis™ mass spectrometer, and the use of the LC-SRM-MS method to quantify nitrosamine impurities in metformin drug products

Conclusions

Quantitation of nitrosamine impurities in metformin drug product below the daily acceptable intake level, meeting both European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) regulatory guidelines. Reproducible and accurate quantitative method suitable for routine screening of nitrosamine impurities in drug products. Use of the Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) for both data collection and processing in compliant environments with full data integrity and security capabilities for cGMP facilities, including 21 CFR part 11.

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Determination of genotoxic nitrosamines in Valsartan with gas chromatography and mass spectrometry

Yanggang Zhang, Jinshui Che, Shen Wang, Thermo Fisher Scientific, Shanghai, China

Keywords
GC-MS, GC-MS/MS, Genotoxic impurities, Headspace, Nitrosamines, NDMA, NDEA, Valsartan, TriPlus 500 HS, TSQ 9000, ISQ 7000

Introduction

This application note covers all the recommended GC-MS methods: liquid injection with single quadrupole GC-MS (CFDA method)1 , headspace injection with single quadrupole GC-MS liquid injection using triple quadrupole GC-MS/MS. All methods were tested for sensitivity, robustness, and regulatory compliance.

- Thermo Scientific™ Trace™ 1310 GC system
- Thermo Scientific™ TriPlus™ 500 Headspace Autosampler
- Thermo Scientific™ ISQ 7000™ Single Quadrupole Mass Spectrometer
- Thermo Scientific™ TSQ 9000™ Triple Quadrupole Mass Spectrometer

Goal

he aim of this work was to evaluate the quantitative performance of Thermo Scientific™ GC-MS solutions in combination with liquid and headspace sampling techniques for the determination of genotoxic nitrosamines in Valsartan according to the Chinese Pharmacopoeia method1 as well as U.S. Food and Drug Administration (U.S. FDA) recommended methodology

Conclusions

All the methods are consistent for the determination of NDMA, while for NDEA the use of GC-MS/MS offers higher sensitivity and more accurate quantitative results.

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Overcoming the challenges of nitrosamine impurities in drugs

Keywords
nitrosamines, pharma, QC, GMP, pharmaceutical impurities, GC, high resolution mass spectrometry, HRMS, Orbitrap Exploris GC, FDA, mutagenic/genotoxic impurities, pharma QC analytical testing laboratories, validation, QC testing, targeted quantification, gas chromatography, Chromeleon CDS

“A challenge with headspace GC-based testing is carryover of residual organic solvents. We found that the TriPlus 500 headspace sampler fully addresses the carryover problem due to directly connecting to the column. TriPlus RSH autosampler is also a great option as it allows a quick switching between headspace and liquid injection modes, significantly increasing our throughput” – Dr. Dujuan Lu (SGS, USA)

“Dealing with nitrosamines impurities in pharmaceutical industry is not a challenge if you have HS-GC-MS/MS TSQ technology. Selectivity and sensitivity to quantitate target volatile nitrosamines at low levels are the key to assure compliance now and for the future.” – Dr. Siva Lakshmi (Laurus Labs, India)

“The Q Exactive GC mass spectrometer coupled with headspace sampler helps us a lot with confident identification of volatile organic compounds (VOCs) due to its excellent mass accuracy down to sub-1 ppm level.” – Dr. Dujuan Lu (SGS, USA)

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Determination of nitrite in pharmaceuticals

Jingli Hu and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA, USA

Keywords

Dionex ICS 6000 HPIC system, Dionex IonPac AS19-4µm column, losartan, metformin, ranitidine, diphenhydramine, ADRS 600 suppressor, ion chromatography, n-nitrosamine, NDMA

Introduction

The use of nitrite in a manufacturing process can represent a risk for NDMA formation if a secondary or tertiary amine is present. Therefore, it is important to limit the nitrite and amine levels in drug substances and drug products.

In this application note an IC-based method is developed to determine the nitrite levels in pharmaceuticals, the separation is achieved by anion-exchange chromatography and detection by UV absorbance at 210 nm. The method was validated and successfully applied to seven pharmaceutical samples, including metformin, losartan, ranitidine, and diphenhydramine.

- Thermo Scientific™ Dionex™ ICS-6000 HPIC system
- Thermo Scientific™ Dionex IonPac AS19-4µm column

Goal

To develop a method to determine nitrite in pharmaceuticals to assess the likelihood of nitrosamine formation

Conclusions

A method was developed for the determination of nitrite in pharmaceuticals by coupling IC with UV absorbance detection. The LOD of nitrite in a pharmaceutical sample is 0.918 ppm (µg/g API). The method is accurate and precise due to the high reproducibility of the Reagent-Free ion chromatography system. This method should be applicable to the determination of nitrite throughout the manufacturing process of a drug product to assess the likelihood of nitrosamine formation.

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Unique tools for impurity analysis

LC-UV is well established but it can't answer all the questions alone. Alternative separation or detection techniques are well suited to answer the questions in front of them, such as organic acid impurities with Ion Chromatography, or being able to measure compounds that other technologies fail to detect with Charged Aerosol Detection. **Click on note titles to jump to page.**

Quantitation of tenofovir and impurities in multi-component drug products by ternary gradient reversed-phase chromatography with charged aerosol detection

Katherine Lovejoy, Thermo Fisher Scientific, Germering, Germany

Keywords
Tenofovir, emtricitabine, charged aerosol detector, uniform response, inverse gradient compensation, impurity profiling, ternary gradient, single-calibrant quantitation

Introduction

In this work, the ability to use an inverse ternary gradient and its application to the analysis of a mixture of antiviral drugs is shown for the first time. With the ternary gradient, CAD quantitative accuracy with and without inverse gradient is compared. Comparison of the quantitative accuracy of the CAD and a UV detector is also evaluated. Finally, a simple strategy to account for salt formation between charged analytes and mobile phase additives (acetate in this example) on detector response is presented.

- Thermo Scientific™ Vanquish™ Flex Duo UHPLC system with Charged Aerosol Detector
- Thermo Scientific™ Accucore™ aQ analytical column

Goal

Demonstrate the implications of salt formation on uniform response when using charged aerosol detection.

Conclusions

Improves single-calibrant quantitation of charged analytes by taking into consideration their salt formation with mobile phase additives. Illustrates the ability to use inverse gradient compensation to normalize detector response when using a ternary (three-eluent) gradient

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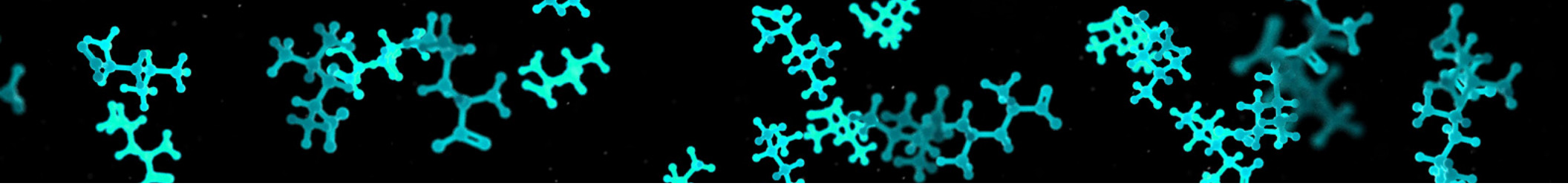

Impurity analysis of L-aspartic acid and glycine by HPLC-UV-CAD

Ruben Pawellek, Adrian Leistner, Ulrike Holzgrabe University of Wuerzburg, Germany

Keywords
Amino acids, impurity analysis, ion pair chromatography, Vanquish Horizon Charged Aerosol Detector, Variable Wavelength Detector

Introduction

This application aims to offer a more reliable alternative method to the compendial methods for the impurity analysis of L-aspartic acid and glycine by high performance liquid chromatography with ultraviolet and charged aerosol detection (HPLC-UV-CAD) methods. The used detection technique enables the quantitation of polar amino acids and related organic acids in a single chromatographic run.

- Thermo Scientific™ Vanquish™ Horizon UHPLC system with Charged Aerosol Detector
- Thermo Scientific™ Acclaim™ PA II analytical column

Goal

Demonstrate that with this approach the currently required two compendial methods for the respective impurity classes could be substituted by a single analysis with comparable LOQs.

Conclusions

Replacement of error-prone derivatization methods by more robust and reliable UV-CAD methods. Simultaneous detection of amino acids and organic acids by a single method instead of two separate methods offering reduced analysis time and costs. Improved sensitivity for weak-chromophoric amino acids by hyphenated detection technologies

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Quantification of paclitaxel, its degradants, and related substances using UHPLC with charged aerosol detection

Michael Menz, Frank Steiner, Thermo Fisher Scientific, Germering, Germany; Ian Acworth, Thermo Fisher Scientific, Chelmsford, MA, USA

Keywords
Vanquish Flex Duo UHPLC, charged aerosol detection, global calibration, impurity analysis, paclitaxel, taxane, forced degradation, stability analysis, inverse gradient

Introduction

In this application note, a Thermo Scientific™ Accucore™ Pentafluorophenyl (PFP) column was used to separate paclitaxel from its related compounds and other impurities. Calibration using standards of paclitaxel and related compounds was used to estimate the quantities of unknown impurities present in the paclitaxel product. A thermal degradation study was also performed with the degradation products being analyzed and subsequently quantified using UHPLC-UV-CAD.

- Thermo Scientific™ Vanquish™ Flex Duo UHPLC system with Charged Aerosol Detector
- Thermo Scientific™ Accucore™ PFP analytical column

Goal

First, to demonstrate the ability to quantify multiple impurities with a single calibrant by using the inherent uniform response of charged aerosol detection (CAD). Second, to highlight the capabilities of the Thermo Scientific™ Vanquish™ Flex Duo UHPLC system to provide inverse gradient compensation, which is essential to achieve reliable single calibrant quantification with CAD.

Conclusions

Uniform response in gradient elution using charged aerosol detection with the Thermo Scientific™ Vanquish™ Flex Duo Inverse Gradient Workflow. Quantification of multiple API-related species by a single calibrant.

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APPLICATION NOTE 73979

LIQUID CHROMATOGRAPHY

Polysorbate 80 profiling by HPLC with mass and charged aerosol detection

Mauro De Pra, Denis A. Ispan, Katherine Lovejoy, Sylvia Grosse, Stephan Meding, Frank Steiner, Thermo Fisher Scientific, Germany

Keywords

Vanquish Flex, Vanquish Duo, ISQ EM, CAD, inverse gradient, Tween, polysorbate, surfactants, formulations, charged aerosol detection, single quadrupole, mass detection, ultra high performance liquid chromatography, excipient

Introduction

An HPLC-CAD method for fingerprinting of PS 80 raw material capable of resolving the components based on the degree of esterification was developed.

- Thermo Scientific™ Vanquish Flex Duo™ UHPLC system with Charged Aerosol Detector
- Thermo Scientific™ ISQ™ EM single quadrupole mass spectrometer
- Thermo Scientific™ Accucore™ C18 150 × 2.1 mm; 2.6 µm LC Column

Goal

Provide an HPLC method suitable for fingerprinting of polysorbate 80 samples and detect variability between different suppliers, grades, and production batches.

Conclusions

The method enables monitoring of different productions, thereby providing a simple, albeit reliable, tool to ensure the consistency of PS 80 raw materials and contribute to consistent drug formulation production. Thanks to the uniform response, CAD with inverse gradient provides the real mass balance between species with different degrees of esterification.

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Impurity analysis of gabapentin by HPLC-UV-CAD

Ruben Pawellek, Adrian Leistner, Ulrike Holzgrabe - Institute of Pharmacy, University of Wuerzburg, Germany

Keywords
Gabapentin, impurity analysis, Vanquish Horizon Charged Aerosol Detector, Variable Wavelength Detector

Introduction

In this application, two Ph. Eur. HPLC-UV-CAD methods were combined for the impurity analysis of gabapentin. This allowed simultaneous determination of the volatile impurity A and the chromophore-deficient impurities B, D, E, and G in one single chromatographic run at a quantitation limit of at least 0.03%.

- Thermo Scientific™ Vanquish™ Flex Binary UHPLC system
- Thermo Scientific™ Vanquish™ Charged Aerosol Detector H

Goal

This application aims to replace the two separate compendial methods for the impurity analysis of gabapentin employed in the European Pharmacopoeia (Ph. Eur.) with one single HPLC method with hyphenated ultraviolet and charged aerosol detectors (UV-CAD).

Conclusions

A simple, rapid, and selective HPLC-UV-CAD method for the impurity profiling of gabapentin was developed. Hyphenation of UV and CAD enabled the simultaneous detection of volatile impurity A and the chromophore-deficient impurities B, D, E, and G in one chromatographic run.

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IC-MS for the determination of organic acids in pharmaceutical solutions

Detlef Jensen, Thermo Scientific GmbH, Dreieich, Germany; Wai-Chi Man, Thermo Scientific, Hemel Hempstead, UK

Keywords
Ion chromatography, IC, suppression, aliphatic and unsaturated, RFIC, Dionex IonPac AS11-HC-4µm, ISQ EC single quadrupole mass spectrometer

Introduction

This application note illustrates the use of an easy-to-implement IC-MS method for the determination of aliphatic and unsaturated organic acids in pharmaceutical solutions. This workflow employs both suppressed conductivity and MS detection to increase the information available from each sample.

- Thermo Scientific™ Dionex™ IonPac™ AS11-HC-4µm column
- Thermo Scientific™ Dionex™ Integrion™ HPIC™
- Thermo Scientific™ ISQ EC single quadrupole mass spectrometer

Goal

To develop a simplified ion chromatography (IC) application in conjunction with mass-selective detection to facilitate the identification and quantification of highly polar aliphatic and unsaturated organic acids in pharmaceutical solutions

Conclusions

This study illustrates the use of a simplified IC-MS method to facilitate the trace amount determination of highly polar, low molecular weight aliphatic and unsaturated organic acids in pharmaceutical solutions. By improving the identification and quantification of these organic acids, pharmaceutical companies can overcome significant challenges in impurity monitoring.

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Validation of an improved ion chromatography method for the limit of choline test in the USP Succinylcholine Chloride monograph

Hua Yang and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
Dionex IonPac CS19 column, suppressed conductivity detection, pharmaceutical, USP monograph, drug substance, drug product, impurity, United States Pharmacopeia, ICS-5000+ , ICS-6000

Introduction
This application note reports the method development and then the evaluation of the improved IC method for the limit of choline test. The evaluation follows the guidelines given by the International Conference on Harmonization (ICH) and the USP, which are outlined in the ICH Guideline Q2A and Q2B Validation of Analytical Procedures, the USP General Chapter Validation of Compendial Methods, and USP General Chapter Chromatography.

- Thermo Scientific™ Dionex™ ICS-5000+ HPIC™ system
- Thermo Scientific™ Dionex™ IonPac™ CS19 anionexchange column (USP L97)
- Thermo Scientific™ Dionex™ CERS™ 500 Cation Electrolytically Regenerated Suppressor for suppressed conductivity detection

Goal
To validate an improved ion chromatography method developed for the limit of choline test in the United States Pharmacopeia (USP) Succinylcholine Chloride monograph

Conclusions
The IC method, with the addition of a 50 mM MSA wash for 18 min to each injection to elute succinylcholine, meets the parameters specified in the USP Succinylcholine Chloride monograph and was validated following USP and ICH guidelines. The study showed that the IC method is reproducible, has a linear calibration, and is sensitive for choline determination in succinylcholine chloride. The method is precise, accurate, and robust. Therefore, it is suitable to replace the current limit of choline method in the Succinylcholine Chloride USP monograph, which was found to be problematic.

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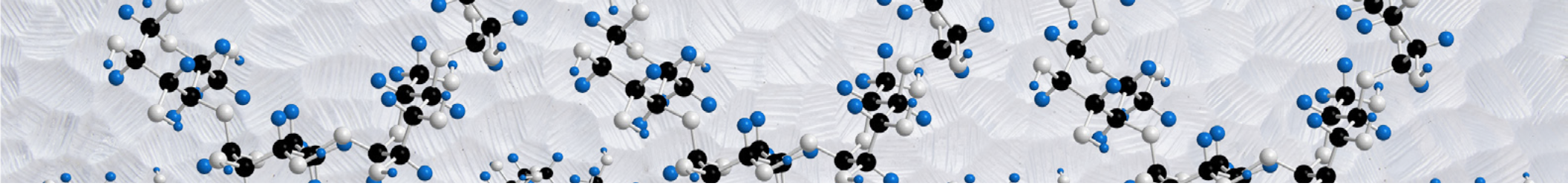

HPAE-PAD determination of cyclodextrins

Manali Aggrawal and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
USP monograph, Betadex sulfobutyl ether sodium, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, Dionex ICS 5000+ system, Dionex ICS 6000 system, excipient, USP-NF, Dionex CarboPac PA200 column

Introduction

The USP-NF Betadex Sulfobutyl Ether Sodium monograph describes an HPAE-PAD method for the determination of β-cyclodextrin impurity in betadex sulfobutyl ether sodium. In this application note, the column is changed to a Thermo Scientific™ Dionex™ CarboPac™ PA200 Analytical and Guard Column, followed by detection using the four-potential waveform with a gold disposable working electrode. Key performance parameters were evaluated and compared including separation, system suitability, linearity, limits of detection, and precision. The percentage of betadex results were compared with the acceptance criteria in the USP monograph. The application of the Dionex CarboPac PA200 column to separating other CDs was also examined.

- Thermo Scientific™ Dionex™ ICS-5000+ system
- Thermo Scientific™ Dionex™ CarboPac™ PA200 analytical column

Goal

To evaluate the Thermo Scientific™ Dionex™ CarboPac™ PA200 column for the separation of α, β, and γ-cyclodextrins and for the determination of β-CD according to the USP Betadex Sulfobutyl Ether Sodium monograph.

Conclusions

HPAE-PAD method was successfully developed using a Dionex CarboPac PA200 column for the separation and determinations of α-, β-, and γ-CDs. The limit of betadex test in the USP Betadex Sulfobutyl Ether Sodium monograph could be successfully performed using the Dionex CarboPac PA200 column. Two commercial betadex sulfobutyl ether sodium samples were tested and found to contain betadex impurity under the specified limit prescribed in the USP monograph. The separation, linearity, reproducibility, and sensitivity were found to meet or exceed the current USP Betadex Sulfobutyl Ether Sodium monograph performance requirements.

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Assay of potassium bitartrate using ion chromatography

Beibei Huang and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
Dionex IonPac AS20 column, suppressed conductivity detection, pharmaceutical, USP Monograph, drug substance, RFIC system

Introduction

The USP has embarked on a global initiative to modernize many of the existing monographs across all compendia. The current USP monograph for potassium bitartrate uses titration to determine the tartrate content. In response to the modernization initiative, we propose a selective and sensitive IC method to replace the titrimetric assay for potassium bitartrate.

- Thermo Scientific™ Dionex™ Integrion™ HPIC™ system
- Thermo Scientific™ Dionex™ IonPac™ AS20 analytical column

Goal

To develop an ion chromatography (IC) method to replace the titrimetric assay for potassium bitartrate in the United States Pharmacopeia (USP) Potassium Bitartrate monograph

Conclusions

This study developed and validated an IC-based assay of potassium bitartrate to modernize the USP Potassium Bitartrate monograph. This method uses a high-performance anion-exchange column to separate tartrate in samples. This 5 min method was validated following the guidelines outlined in USP General Chapter, Validation of Compendial Methods. Compared to the time-consuming assay in the USP Potassium Bitartrate monograph, this IC-based assay executed with an RFIC system offers a simple, accurate, and robust measurement of the analyte instead of titration with sodium hydroxide that the current USP technique uses and without manual mixing of hazardous reagents.

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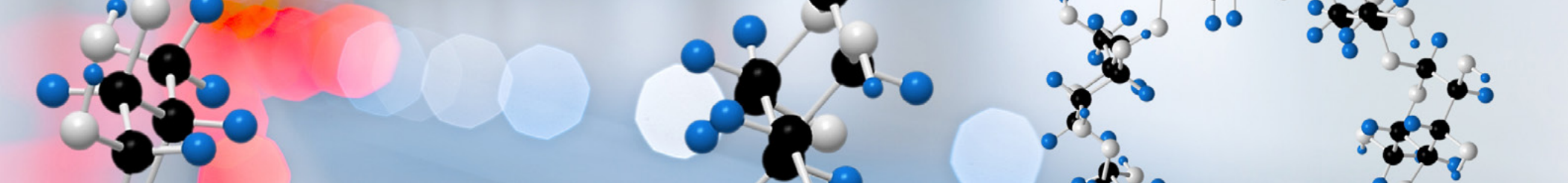

Limit of β-cyclodextrin (betadex) in betadex sulfobutyl ether sodium

Manali Aggrawal and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
USP monograph, HPAE-PAD, cyclodextrin, Dionex IonPac AS11 column, Dionex ICS-5000+ HPIC system, Dionex ICS-6000 HPIC system, excipient, USP-NF

Introduction

In this application note, we evaluated the USP monograph method for separation of Betadex sulfobutyl solution. The method was further evaluated with the 4-potential waveform recommended for carbohydrates and a gold disposable working electrode (DE). In this additional evaluation, only the waveform was changed compared to the monograph method. Key performance parameters were evaluated including separation, system suitability, linearity, limits of detection, and precision. Two samples were analyzed. The percentage of betadex results were compared with the acceptance criteria in the USP monograph.

- Thermo Scientific™ Dionex™ ICS-5000+ HPIC™ system
- Thermo Scientific™ Dionex™ IonPac™ AmG analytical column

Goal

To evaluate the limit test for β-cyclodextrin in the USP Betadex Sulfobutyl Ether Sodium monograph and to evaluate the same limit test with the 4-potential waveform recommended for carbohydrate detection and a disposable working electrode

Conclusions

Determination of β-cyclodextrin could be successfully performed using the USP Betadex Sulfobutyl Ether Sodium monograph conditions. Two commercial betadex sulfobutyl ether sodium samples were tested and found to contain betadex impurity under the specified limit prescribed in the USP monograph. We also demonstrated that this method could be executed with two different 4-potential waveforms and a disposable gold electrode on a PTFE substrate with comparable results. The separation, linearity, reproducibility, and sensitivity were found to meet or exceed the current USP Betadex Sulfobutyl Ether Sodium monograph performance requirements.

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Determination of ammonia impurity in potassium bitartrate using ion chromatography

Beibei Huang and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
Dionex IonPac CS16 column, suppressed conductivity detection, pharmaceutical, USP Monograph, drug substance, RFIC system

Introduction

In this application note we propose a selective and sensitive IC method to replace the colorimetric test for the determination of ammonia impurity in potassium bitartrate. The applied Reagent-Free™ Ion Chromatography (RFIC) system requires only deionized (DI) water as the carrier, it significantly simplifies system operation and improves analytical reproducibility. The linearity, precision, accuracy, ruggedness, and the limits of detection (LODs) and quantitation (LOQs) of this 5 min method are validated following the guidelines outlined in USP General Chapter , Validation of Compendial Methods.

- Thermo Scientific™ Dionex™ ICS-6000 HPIC system
- Thermo Scientific™ Dionex IonPac CS16 column

Goal

To develop a sensitive and robust ion chromatography (IC)-based test for the determination of ammonia impurity in potassium bitartrate to modernize the test in the United States Pharmacopeia's (USP) Potassium Bitartrate monograph

Conclusions

The high-capacity Dionex IonPac CS16 column is ideal for impurity testing. This test method is capable of determining ammonia with good accuracy and precision at its limit (in the current USP monograph) in potassium bitartrate. This 5 min method was validated following the guidelines outlined in USP General Chapter , Validation of Compendial Methods. The method is calibrated in the range 0.01 to 1 mg/L (r2 = 1.0, quadratic fitting), precise with low retention time and peak area RSDs (r2 = 1.0, quadratic fitting), precise with low retention time and peak area RSDs (

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Determination of methanesulfonic acid in busulfan by ion chromatography

Manali Aggrawal and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA, USA

Keywords
USP monograph, Dionex IonPac AS11-HC column, Dionex ICS-5000+ system, Dionex ICS-6000 system, USP-PF, MSA

Introduction

In this application note, we evaluated the proposed USP Busulfan monograph method for the “Limit of Methanesulfonic Acid”, which uses an ion chromatography based method. Key performance parameters were evaluated including separation, system suitability, linearity, limit of detection, and precision. Three busulfan samples were analyzed. The percentage of MSA results were compared with the acceptance criterium in the proposed USP monograph.

- Thermo Scientific™ Dionex™ ICS-6000 HPIC system
- Thermo Scientific™ Dionex IonPac AS11-HC

Goal

To evaluate the limit test for MSA in the proposed USP Busulfan monograph

To evaluate the same limit test with modifications

Conclusions

In this application note, we demonstrated that the limit of MSA in the busulfan method could be successfully performed using the proposed USP Busulfan monograph conditions. Three commercial busulfan samples were tested and one sample was found to contain MSA impurity above the specified limit prescribed in the proposed USP monograph. We also demonstrated that this method could be executed with a modified method with comparable results. The modified method allows more time between sample preparation and analysis by better conserving sample integrity. The separation, linearity, reproducibility, and sensitivity were found to meet or exceed the proposed USP Busulfan monograph performance requirements.

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Determination of inorganic anion impurities in a water-insoluble pharmaceutical by ion chromatography with suppressed conductivity detection

Manali Aggrawal and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA, USA

Keywords

USP monograph, Dionex IonPac AS11-HC column, Dionex ICS-5000+ system, Dionex ICS-6000 system, USP-PF, MSA

Introduction

In this application note we demonstrate the development of an IC method for the determination of anionic impurities in a proprietary water-insoluble pharmaceutical. The linearity, detection limits, precision, and accuracy of the method are described.

- Thermo Scientific™ Dionex™ ICS-3000 Reagent-Free™ Ion Chromatography (RFIC™) system*

Conclusions

In this AN, we demonstrated the ability to determine trace anions in a proprietary water-insoluble pharmaceutical using preconcentration with matrix elimination. This method was designed to provide a simpler approach that avoids the potential complications of column contamination and excess column backpressure that can occur when analyzing water-insoluble samples. The use of a hydroxideselective Dionex IonPac AS15 column provided an efficient separation of common anions from low to high µg/L concentrations that are typically found in pharmaceuticals. In addition, the combination of a hydroxide-selective column with an electrolytically generated potassium hydroxide eluent eliminates the problems associated with the manual preparation of hydroxide eluents and therefore further increases the ease-of-use and method automation. This method demonstrated good linearity, sensitivity, precision, and accuracy for determining inorganic anion impurities in a water-insoluble pharmaceutical compound

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Magnesium oxide monograph modernization with ion chromatography

Manali Aggrawal and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
USP monograph, Dionex IonPac CS16 column, Dionex ICS 6000 system, USP-NF, calcium carbonate

Introduction

The United States Pharmacopoeia (USP) monograph for MgO describes an assay based on titration. As part of monograph modernization efforts, the USP proposed a single ion chromatography (IC) method to replace the titration procedure used for the MgO assay and a wet chemical method used for the Limit of Calcium test. Key performance parameters were evaluated, including separation, system suitability, linearity, limit of detection, and precision.

- Thermo Scientific™ Dionex™ ICS-6000 HPIC system
- Thermo Scientific™ Dionex IonPac™ CS16, Analytical, 5 × 250 mm
- Thermo Scientific™ Dionex IonPac™ CG16, Guard, 5 × 50 mm

Goal

To evaluate the ion chromatography methods for the Magnesium Oxide assay and the Limit of Calcium test in the proposed United States Pharmacopeia Magnesium Oxide monograph revision

Conclusions

The separation, linearity, reproducibility, and sensitivity were found to meet or exceed the proposed USP Magnesium Oxide monograph revision performance requirements.

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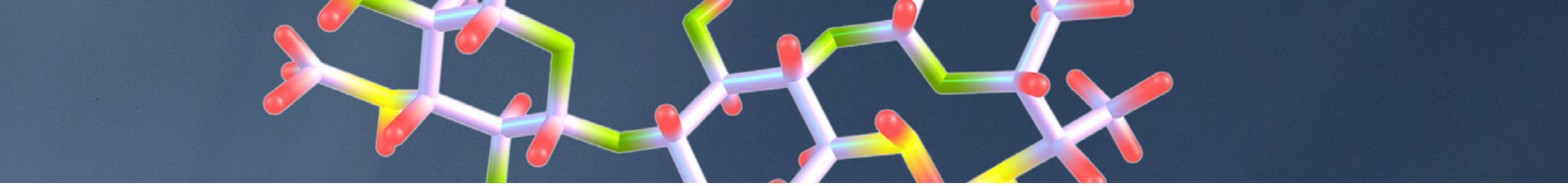

Determination of gentamicin and related impurities in gentamicin sulfate

Jingli Hu and Jeffrey Rohrer, Thermo Fisher Scientific, Sunnyvale, CA

Keywords
Dionex IonPac AmG-3µm C18 column, aminoglycoside, Dionex ICS 5000+ HPIC system, PAD, electrochemical detection, drug substance, antibiotic, ion-pair reversed-phase HPLC, USP, EP, Dionex ICS-6000

Introduction

In this application note, the gentamicin sulfate analysis in the USP monograph was evaluated with a Dionex IonPac AmG-3µm C18 column using a 4-potential waveform for electrochemical detection of carbohydrates. Other than the waveform, the method and conditions were exactly as described in the USP Gentamicin Sulfate monograph. Key performance parameters were evaluated including system suitability separation, linearity, limits of detection, and precision. Impurity results were compared with EP Gentamicin Sulfate monograph and USP Gentamicin Sulfate in-process revision monograph's acceptance criteria.

- Thermo Scientific™ Dionex™ ICS-5000+ HPIC™ system
- Thermo Scientific™ Dionex IonPac AmG-3µm C18 column
- Thermo Scientific™ Dionex™ ICS-5000+ ED Electrochemical Detector

Goal

To validate the gentamicin sulfate United States Pharmacopeia (USP) monograph method for gentamicin composition and impurities using a Thermo Scientific™ Dionex™ IonPac™ AmG-3µm C18 column

Conclusions

This application note demonstrates that the USP Gentamicin Sulfate monograph Content of Gentamicins method and the USP in-process revision Gentamicin Sulfate monograph method for organic impurities method could be successfully executed as described in the USP and EP monographs. The separation, linearity, reproducibility, and sensitivity were found to meet or exceed the current USP/EP Gentamicin Sulfate monograph performance requirements.

See also APPLICATION UPDATE 72648 Determination of gentamicin and related impurities in gentamicin sulfate using simple eluents

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Updated elemental, residual solvent and E&L workflows

Quality control (QC) testing of pharmaceuticals is more than final product impurity testing. It must be rigorous and involves multiple techniques including GC-MS and LC-MS, and elemental analysis techniques. Impurities can take many forms, from solids to volatiles and everything in between. We updated solutions for pharmaceutical testing organizations conducting small molecule impurities; from heavy metals to extractables and leachables.

Click on note titles to jump to page.

Analysis of elemental impurities in drug products using the Thermo Scientific iCAP 7400 ICP-OES Duo

Sanja Asendorf, Thermo Fisher Scientific, Bremen, Germany

Keywords

Drug products, Elemental impurities, ICH Q3D, Metals, Pharmaceutical, USP 232, USP 233

Introduction

In future all drug products produced and sold in the U.S. must comply with the limits set by USP General Chapter <232> . Drug substances and excipients will be tested and reported for elemental impurities. Similarly, nutraceutical products must comply with the limits set by USP General Chapter <2232>, which extends only to arsenic, mercury, cadmium and lead. Speciation of organic and inorganic elemental forms is critical for the analysis of Dietary Supplements. The iCAP 7400 ICP-OES Duo is well suited to this type of application due to its low detection capabilities for the elements of interest, as well as for its ability to resolve complex spectra. Both points are critical in relation to the low limits stipulated for elements such as arsenic and mercury.

- Thermo Scientific™ iCAP™ 7400 ICP-OES

Goal

Trace elemental impurities in pharmaceutical products are potentially harmful and thus their determination is of great importance. The work described here demonstrates compliance with 21 Code of Federal Regulation (CFR) Part 11 and analysis according to latest implementation of United States Pharmacopeia (USP) General Chapters <232> and <233>.

Conclusions

The analysis shows that the Thermo Scientific iCAP 7000 Plus Series ICP-OES delivers excellent accuracy and sensitivity for analyses of trace elements and major components in drug products in conformity with the present USP General Chapters Elemental Impurities – Limits and Elemental Impurities - Procedures. The results obtained prove the excellent ability of the instrument to resolve complex sample spectra, and the achieved detection limits demonstrate the suitability of the instrument to analyze toxic trace elements like arsenic and mercury for which the stipulated limits are very low.

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Analysis of pharmaceutical products for their elemental impurities with the Thermo Scientific iCAP RQ ICP-MS

Julian Wills and Daniel Kutscher, Thermo Fisher Scientific, Bremen, Germany

Keywords

FDA 21 CFR part 11, Microwave digestion, Pharmaceutical compliance, Pharmaceutical preparations, United States pharmacopeia, USP 232, USP 233

Introduction

This note describes the effective application of the Thermo Scientific™ iCAP™ RQ single quadrupole (SQ) ICP-MS, to the detection and quantification of the 15 target elements specified in USP , in accordance with the ICP-MS procedures described in USP. In order to generate data compliant with the procedures described in 21 CFR Part 11, the Thermo Scientific Qtegra™ Intelligent Scientific Data Solution™ (ISDS) Software includes comprehensive features for the pharmaceutical industry, such as user access levels, audit trails, support for electronic signatures as well as integrated, secure data management.

- Thermo Scientific™ iCAP™ RQ ICP-MS system

Goal

To demonstrate the use of the Thermo Scientific™ iCAP™ RQ ICP-MS to accurately determine concentrations of elemental impurities in pharmaceutical products brought into solution using microwave digestion. All sample preparation, measurement and data evaluation to be compatible with the guidelines defined in USP chapters Elemental Impurities – Limits and Elemental Impurities – Procedures

Conclusions

This application note has shown that the iCAP RQ ICP-MS is an ideal tool for elemental determination in pharmaceutical products after dissolution by microwave digestion. For the three drugs tested, method detection limits fifty times lower than the target limits were produced showing that the iCAP RQ ICP-MS is easily capable of accurately and precisely measuring all fourteen of the specified elements at the target limits listed in USP .

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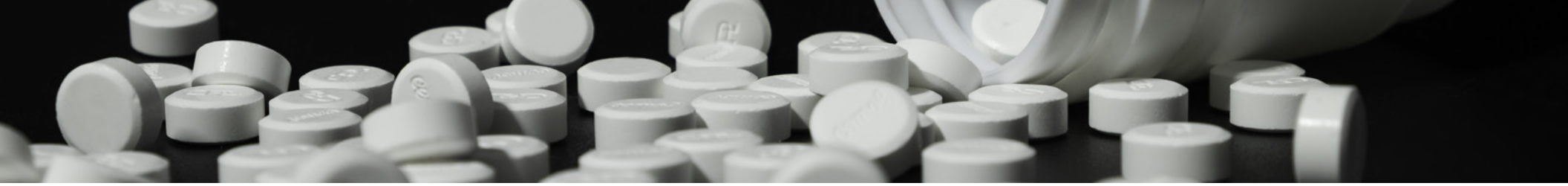

Simplified, cost-effective headspace GC method for residual solvents analysis in pharmaceutical products

Giulia Riccardino, Cristian Cojocariu, Thermo Fisher Scientific, UK

Keywords

USP , residual solvents, pharmaceuticals, valve-and-loop, static headspace, HS, gas chromatography, GC, flame ionization detector, FID, TriPlus 500 Headspace Autosampler

Introduction

Organic solvents are often used in the manufacturing and purification of drug substances but due to their potential toxicity their absence/presence must be verified in the pharmaceutical products to ensure patient safety. The United States Pharmacopeia (USP) method 1 provides detailed procedures for screening, confirmation and quantitation of residual solvents, including sample preparation and analytical conditions.

- Thermo Scientific™ Trace™ 1310 GC system
- Thermo Scientific™ TriPlus™ 500 Headspace Autosampler
- Thermo Scientific™ TraceGOLD™ TG-624™ GC Column

Goal

The aim of this work was to develop a rapid, cost-effective, modified USP HS-GC-FID method for residual solvent determination in pharmaceutical products using the Thermo Scientific™ TriPlus™ 500 Headspace Autosampler and nitrogen as carrier gas.

Conclusions

The results of this study demonstrate that a rapid (×7 improvement in analysis speed) with a cost-effective nitrogen carrier gas can be achieved whilst meeting USP resolution requirements..

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Pharma materials study: GC-MS identification of extractables and leachables from elastomer material

Bénédicte Gauriat[1], Isabelle Froger[2], Damien Chevaillier[2], Hans-Joachim Huebschmann[3]
[1]Thermo Fisher Scientific, Les Ulis, France; [2]Septodont, Dental Pharmaceutical Company, Saint-Maur-des-Fossés, France; [3]Thermo Fisher Scientific, Singapore

Keywords
Pharmaceutical products, Leachables, Extractables, GC-MS, Deconvolution, Unknown screening, ISQ 7000

Introduction

This application note describes a part of an extractable analysis of an elastomeric plunger considered for potential use in a dental injectable cartridge using different extraction techniques, derivatization and HS analysis by single quadrupole GC-MS. A parallel classical flame ionization detection (FID) channel was configured for use in a future routine method, if required. While the composition of the plunger is known from the manufacturer, the drug product manufacturer has very little information about its composition and consequently about the substances that might migrate into the applied medicine

- Thermo Scientific™ TRACE™ 1310 Gas Chromatograph
- Thermo Scientific™ ISQ™ Series Single Quadrupole GC-MS System
- Thermo Scientific™ TriPlus™ RSH Autosampler

Goal

To identify potential extractables and leachables from elastomeric plungers with gas chromatography with parallel with FID and MS detection. The deconvoluted spectra to be checked against NIST library for identification, or else realistic structure proposal by Thermo Scientific™ Mass Frontier™ software.

Conclusions

Parallel detection using full-scan MS and FID shows very good compliance in the detected compound pattern. After identification of typical major components using the mass spectrometer, routine analysis for such compounds can be run reliably using FID. The complete analytical system using the ISQ as a single quadrupole MS with the parallel FID on the TRACE 1310 GC system, associated with acquisition and processing software, is a powerful and easy-to-use solution for the identification of unknowns, routine screening, and if required, also compound quantitation for product safety control and similar quality control applications.

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Analytical Solutions to Challenges in Headspace GC-MS Analysis of Volatile Extractable and Leachable Compounds

Dujuan Lu, Danny Hower, SGS Fairfield, USA
Daniela Cavagnino, Cristian Cojocariu, Thermo Fisher Scientific, UK

Keywords
Extractables and leachables, E&L, Orbitrap GC-MS, HRAM, valve and loop, static headspace, gas chromatography, GC, gas chromatography-mass spectrometry, GC-MS, flame ionization detector, FID

Introduction

This work highlights the simplicity of the static headspace method set up and optimization, making this sampling technique very suitable and convenient for the study of volatiles extractables in polymeric materials.

- Thermo Scientific™ Trace™ 1310 GC system
- Thermo Scientific™ Q Exactive™ GC Orbitrap™ GC-MS/MS Mass Spectrometer
- Thermo Scientific™ TraceGOLD™ TG-624™ GC Column

Goal

To demonstrate the advantages of using GC HRAM for the analysis of unknown extractables and leachables.

Conclusions

The results of this study demonstrate that the integration of the TriPlus 500 Headspace Autosampler with the Q Exactive GC Orbitrap mass spectrometer and TraceFinder software is a powerful solution for extracting, profiling, and identifying unknown peaks in complex samples.

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