Analytica Chimica Acta 870 (2015) 29–44

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Tutorial

Tutorial review on validation of liquid chromatography–mass spectrometry methods: Part I

Anneli Kruve [a], Riin Rebane [a], Karin Kipper [a], Maarja-Liisa Oldekop [a], Hanno Evard [a], Koit Herodes [a], Pekka Ravio [b], Ivo Leito [a,*]

[a] University of Tartu, Institute of Chemistry, Ravila 14a, 50411 Tartu, Estonia
[b] Finnish Customs Laboratory, Tekniikantie 13, PL 53, FI-02151 Espoo, Finland

HIGHLIGHTS

- The status of validation of LC–MS methods is comprehensively reviewed.
- Clarity is brought into validation-related terminology.
- Recommendations on difficult validation-related issues in LC–MS are given.

GRAPHICAL ABSTRACT

ARTICLE INFO

Article history:
Received 4 June 2014
Received in revised form 31 January 2015
Accepted 9 February 2015
Available online 13 February 2015

Keywords:
Liquid chromatography–mass spectrometry

ABSTRACT

This is the part I of a tutorial review intending to give an overview of the state of the art of method validation in liquid chromatography mass spectrometry (LC–MS) and discuss specific issues that arise with MS (and MS/MS) detection in LC (as opposed to the "conventional" detectors). The Part I briefly introduces the principles of operation of LC–MS (emphasizing the aspects important from the validation point of view, in particular the ionization process and ionization suppression/enhancement); reviews the main validation guideline documents and discusses in detail the following performance parameters: selectivity/specificity/identity, ruggedness/robustness, limit of detection, limit of quantification, decision limit and detection capability. With every method performance characteristic its essence and

Abbreviations: APCI, atmospheric pressure chemical ionization; API, atmospheric pressure ionization; APPI, atmospheric pressure photo ionization; b_{an}, the slope of the calibration function for the analyte; b_{int}, the slope for the potential interferent; CC_α, decision limit; CC_β, detection capability; EMA/EMEA, European Medicines Agency; ESI, electrospray ionization; E_x, effect of variation of parameter X; FDA, United States Food and Drug Administration; HRMS, high resolution mass spectrometer; ICH, International Conference on Harmonization; IR, infrared spectroscopy; IUPAC, International Union of Pure and Applied Chemists; LC–MS, liquid chromatography–mass spectrometry; LLE, liquid–liquid extraction; LoD, limit of detection; LoQ, limit of quantitation; LRMS, low resolution mass spectrometer; $ME_{ionization}$, matrix effect of ionization; MRM, multiple reaction monitoring; MS/MS, tandem mass spectrometry; MS^n, consequent reaction monitoring; NLS, neutral loss scan; NMR, nuclear magnetic resonance; R_s, chromatographic resolution; RSD, relative standard deviation; s, standard deviation; SPE, solid phase extraction; SRM, selected reaction monitoring; TOF, time-of-flight; UPLC/UHPLC, ultra-high performance liquid chromatography; UV–vis, ultraviolet–visible spectrophotometry; VIM, International Vocabulary of Metrology; α, probability of a blank sample being considered as a positive sample; β, probability of falsely negative result.

The other part of this paper is published here http://dx.doi.org/10.1016/j.aca.2015.02.016

* Corresponding author. Tel.: +372 7 375 259; fax: +372 7 375 264.

http://dx.doi.org/10.1016/j.aca.2015.02.017
0003-2670/

Validation
Electrospray
Ionization suppression
Limit of detection
Robustness

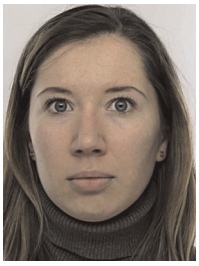
terminology are addressed, the current status of treating it is reviewed and recommendations are given, how to determine it, specifically in the case of LC–MS methods.

Contents

Anneli Kruve obtained her Ph.D. from University of Tartu (UT) in 2011. Since 2005 she has been involved in HPLC and LC/MS method development and validation in various fields: bioanalysis, food analysis as well as industrial analysis. Starting from 2011 she works as a research fellow at UT Institute of Chemistry. In 2008 and 2009 she has worked in University of Helsinki in the field on miniaturization of MS ion sources. Her main research fields are method development for pesticide analysis, fundamental studies of ionization efficiency and design of MS ionization sources.

Riin Rebane obtained her Ph.D. in analytical chemistry from University of Tartu in 2012 with a topic on optimization and validation of liquid chromatographic methods with mass spectrometric detection containing derivatization. For the past eight years her main research area has been LC–MS analysis, including method development and validation for various analytes and development of novel derivatization reagents for LC–MS. She also works as a quality assurance specialist in the Estonian Environmental Research Centre.

Karin Kipper obtained her Ph.D. from University of Tartu (UT) in 2012. Since 2004 she has been involved in the bioanalytical method development and validation for HPLC-UV/vis and LC–MS analysis, working at UT Institute of Pharmacology and Institute of Chemistry. Starting from 2012 Karin Kipper works as a research fellow at UT Institute of Chemistry. Her main research fields are pharmaceutical bioanalysis (pharmacokinetic/pharmacodynamic studies), pharmaceuticals' pathways in environment and development of novel eluent additives for LC–MS in order to improve separation and peak shape of basic compounds.



Maarja-Liisa Oldekop obtained her M.Sc. from University of Tarty (UT) in 2013 and is now a Ph. D. student in the chair of analytical chemistry at UT. Her main field of research is development of LC–MS methods using derivatization. The focus is on matrix influences on this type of analysis, stressing the importance of trueness of the analysis results but also the sensitivity of the method. Since the beginning of 2013 Maarja-Liisa Oldekop works as the quality manager of the UT Testing Centre, which is an ISO/IEC 17025 accredited testing and calibration laboratory.