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www.elsevier.com/locate/talanta

PII: S0039-9140(17)31131-1
DOI: https://doi.org/10.1016/j.talanta.2017.11.005
Reference: TAL18067

To appear in: *Talanta*

Received date: 18 September 2017
Revised date: 30 October 2017
Accepted date: 3 November 2017

Cite this article as: Zhigang Luo, Jingjing He, Jiuming He, Lan Huang, Xiaowei Song, Xin Li and Zeper Abliz, Quantitative analysis of drug distribution by ambient mass spectrometry imaging method with signal extinction normalization strategy and inkjet-printing technology, *Talanta,* https://doi.org/10.1016/j.talanta.2017.11.005

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ABSTRACT

Quantitative mass spectrometry imaging (MSI) is a robust approach that provides both quantitative and spatial information for drug candidates' research. However, because of complicated signal suppression and interference, acquiring accurate quantitative information from MSI data remains a challenge, especially for whole-body tissue sample. Ambient MSI techniques using spray-based ionization appear to be ideal for pharmaceutical quantitative MSI analysis. However, it is more challenging, as it involves almost no sample preparation and is more susceptible to ion suppression/enhancement. Herein, based on our developed air flow-assisted desorption electrospray ionization (AFADESI)-MSI technology, an ambient quantitative MSI method was introduced by integrating inkjet-printing technology with normalization of the signal extinction coefficient (SEC) using the target compound itself. The method utilized a single calibration curve to quantify multiple tissue types. Basic blue 7 and an antitumor drug candidate (S-(+)-deoxytylophorinidine, CAT) were chosen to initially validate the feasibility and reliability of the quantitative MSI method. Rat tissue sections (heart, kidney, and brain) administered with CAT was then analyzed. The quantitative MSI analysis results were cross-validated by LC-MS/MS analysis data of the same tissues. The consistency suggests that the approach is able to fast obtain the quantitative MSI data without introducing interference into the *in-situ* environment of the tissue sample, and is potential to provide a high-throughput, economical and reliable approach for drug discovery and development.

Keyword: Ambient; Air flow assisted ionization; Mass spectrometry imaging; Pharmaceutical quantitative analysis; Signal extinction normalization; Inkjet-printing

Introduction

Understanding the pharmacological or toxicological effects of drug candidates is important, especially during the early stages of drug development [1, 2]. Quantification of targeted drug candidates in tissue sections along with information on their spatial distribution is essential for pharmacokinetic and pharmacodynamics studies of a drug's ADME (absorption, distribution, metabolism, and excretion) characterization [3, 4]. Quantitative whole-body autoradiography (QWBA) [5] and LC-MS/MS [6] are traditional quantitative techniques for biomedical analysis. Compared with QWBA and LC-MS/MS, mass spectrometry imaging (MSI) has the advantage of being able to distinguish the distribution of a drug and its metabolites with the corresponding spatial location without radiolabeling, and has been substantially developed for applications in the field of drug development, along with various ionization methods were utilized [7-12]. However, due to high dependence of the ion signal on the localized environment, quantitative MSI has to face the challenges of the intact tissues analysis, including substance-specific extraction, heterogeneous ionization, tissue-specific ion suppression, and matrix-specific deposition [13, 14], which lead to the mismatch between signal and content. The development of quantitative MSI approaches would promote giant leap forward for the growing requirement of quantitative information, especially for drug discovery and development [14-17].

Matrix-assisted laser desorption/ionization (MALDI) [4, 17, 18] is well-developed technique for quantitative MSI analysis. While, ambient ionization methods, especially spray-based ionization (e.g. DESI) which has the characteristics of soft ionization, easy implementation, and no organic matrix interference, appear to be ideal for pharmaceutical quantitative MSI analysis. However, these ambient mass spectrometry techniques are more susceptible to ion suppression/enhancement [19, 20], and the tissue-specific ion suppression effect still provides challenges for the quantitative MSI analysis [13]. To be certain of the accuracy of the image data created in MSI experiments, a basic requirement is the normalization of signal suppression/enhancement from the ionization environment with ideal compound. Although stable isotope standards are thought to be essential for quantitative analysis, during the discovery stage of pharmaceutical research the synthesis of radiolabeled forms of a large number of drug candidates is not time- or cost-effective [4], which is usually unavailable in the early drug discovery phase. Furthermore, it is impossible to incorporate an internal standard in a tissue section without inducing a physicochemical change [13].