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Dopant-assisted photoionization positive ion mobility spectrometry coupled with time-resolved purge introduction for online quantitative monitoring of intraoperative end-tidal propofol

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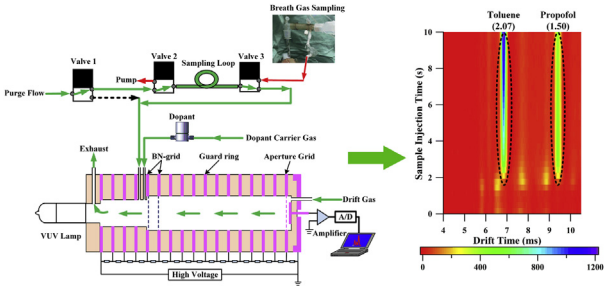
HIGHLIGHTS

- A dopant-assisted photoionization positive ion mobility spectrometry for selective and sensitive detection of propofol.
- Time-resolved purge introduction for eliminating the moisture interference in exhaled breath.
- Accurate quantitative detection of propofol at wide reactant ions intensities with LOQ reaching 0.2 ppbv.
- Online high frequency monitoring of intraoperative end-tidal propofol.

GRAPHICAL ABSTRACT



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ABSTRACT

Online monitoring of end-tidal propofol provides important information of anesthesia deepness for anesthetists as propofol concentrations in plasma and breath are well correlated. In this work, a dopant-assisted photoionization positive ion mobility spectrometry (DAPI-PIMS) coupled with time-resolved purge introduction was developed for online quantitative monitoring end-tidal propofol. With optimized dopant, toluene, the selectivity and sensitivity of propofol was improved as interference from sevoflurane was eliminated. Using the time-resolved purge introduction, the response of propofol and moisture was separated due to their absorption differences on the inwall of the fluorinated ethylene propylene (FEP) sample loop, ensuring sensitive measurement of end-tidal propofol with a short response time of 4 s. The quantitative equation derived from the second order reaction kinetics model extended the quantitative range of propofol from 0.2 ppbv to 45 ppbv. Finally, the method was used to monitor the intraoperative end-tidal propofol of six patients, and the results nicely demonstrated its feasibility in practical clinical environment.

1. Introduction

Propofol is a commonly used intravenous anesthetic with the advantages of short duration, quick recovery for patients [1].

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Sevoflurane is an inhaled anesthetic with a low gas partition coefficient (0.69) [2]. In balanced anesthesia, propofol and sevoflurane were often used in combination to achieve a better anesthetic effect [3]. Propofol is detectable in patients' breath over the clinically relevant range of 0–39 ppbv [4,5]. Online measurement of exhaled propofol could make possible an objective measure of the depth of anesthesia to complement existing clinical observations, as propofol concentrations in plasma and breath are well correlated [6–8]. Thus, rapid response time, high selectivity and sensitivity measuring methods are needed for closed-loop target controlled infusion (TCI) anesthesia with propofol.

So far, various methods such as proton transfer reaction-mass spectrometry (PTR-MS) [7,8], ion molecular reaction-mass spectrometry (IMR-MS) [9–11], electron ionization-mass spectrometry (EI-MS) [1,12], selected ion flow tube-mass spectrometry (SIFT-MS) [13], gas chromatography-mass spectrometry (GC-MS) [14–17], and photoacoustic spectroscopy (PAS) [18], have already been used to detect and quantify propofol in exhaled breath. These investigations showed close relations of propofol concentrations in exhaled breath and blood. However, these methods are unsuitable for daily clinical anesthesia in the operating room as the instruments used are complex, bulky, and expensive [19].

Ion mobility spectrometry (IMS), with advantages of high sensitivity, rapid response, low cost and good portability, has been developed as noninvasive analysis methods for clinical application, especially in exhaled breath for the diagnosis of diseases or measurement of exposure to anesthetic gases, such as propofol, sevoflurane, and enflurane [6,19]. Kreuder et al. firstly reported the measurement of propofol by ^{63}Ni-IMS in both positive and negative modes [20]. It was found, that the detection limit in the negative mode is lower as in the positive mode. Then, Zhou et al. reported that in negative mode ^{63}Ni-IMS with reactant ion of $O_2^-(H_2O)_n$, propofol formed three kinds of product ions $(M-H)^-$, $M\cdot O_2^-$, and $(M_2-H)^-$ [21,22]. The linear response range for propofol was achieved to be 0.2–20 ppbv with a limit of detection (LOD) of 65 pptv. However, the radioactivity of ^{63}Ni source limits its clinical application due to safety, environmental, and regulatory concerns. Besides, the anesthesia was not only a total intravenous anesthesia (TIVA) environment, it was often combined with sevoflurane in the practical monitoring process [23]. In negative mode the strong signal response of sevoflurane seriously interfered with the quantitative determination of exhaled propofol. Dopant is usually used for improving the selectivity and sensitivity in dopant-assisted photoionization ion mobility spectrometry [24,25]. However, its application in the analysis and online monitoring of exhaled propofol is rarely reported.

In addition, the high moisture in exhaled breath made the ion mobility spectrum complex and seriously interfered with the detection of propofol [26]. Recently, in order to eliminate the interference of exhaled moisture, IMS coupled with a variety of sampling methods has been developed for exhaled propofol measurement. Baumbach et al. developed multicapillary column ion mobility spectrometry (MCC-IMS) to measure exhaled propofol in a humid environment [5,6,27–29]. Zhou et al. developed membrane inlet and time-resolved dynamic dilution ion mobility spectrometry for detecting propofol with high moisture level [26,30,31]. However, these methods all require a response time of several minutes, which does not meet the requirement of online analysis of intraoperative end-tidal propofol.

In this paper, a dopant-assisted photoionization positive ion mobility spectrometry (DAPI-PIMS) coupled with time-resolved purge introduction was developed for the online quantitative monitoring of intraoperative end-tidal propofol. Through the optimization of dopants, the selectivity and sensitivity of propofol was improved as the interference of sevoflurane was eliminated. Furthermore, the influence of exhaled moisture could be eliminated well by the time-resolved purge introduction method. The exhaled breath was sent into the IMS device through the sample loop with a response time of 4 s. In addition, the second order reaction kinetics quantitative model of propofol quantitation was established and extended the quantitative range of propofol of 0.2 ppbv–45 ppbv. Finally, this method was tested on six patients to online measure intraoperative exhaled propofol, which demonstrated its feasibility in practical clinical environment.

2. Experimental

2.1. Apparatus

A DAPI-PIMS coupled with time-resolved purge introduction built up in our lab was used to conduct the experiments, as shown in Fig. 1. It had a reaction region of 25 mm long and a drift region of 77 mm long. The inner diameters of the two regions were 14 mm and 30 mm. A drift field of 404 V cm^{-1} was applied across the drift

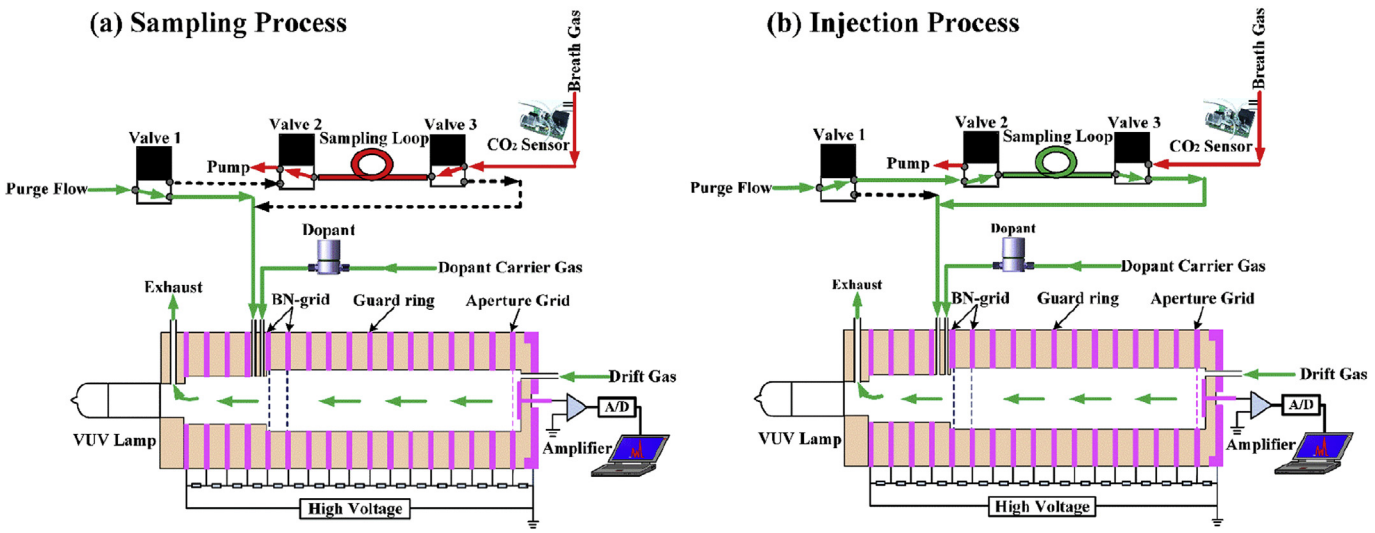

Fig. 1. Schematic of the dopant-assisted photoionization positive ion mobility spectrometry coupled with time-resolved purge introduction at (a) the sampling process and (b) the injection process.

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