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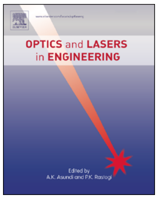

# Sensor for headspace pressure and $H_2O$ concentration measurements in closed vials by tunable diode laser absorption spectroscopy

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ABSTRACT

The concentration of $H_2O$ and the pressure in the headspace of vials are simultaneously measured by a tunable diode laser sensor based on absorption spectroscopy techniques. The 7168.437 $cm^{-1}$ spectral line of $H_2O$ is chosen as the sensing transition for its strong absorption strength and being reasonably far away from its neighboring molecular transitions. In order to prevent interference absorption by ambient water vapor in the room air, a difference between the measured signal and the referenced signal is used to calculate the pressure and $H_2O$ concentration in the headspace of vials, eliminating the need for inert gas purges and calibration with known gas. The validation of the sensor is conducted in a static vial, yielding an accuracy of 1.23% for pressure and 3.81% for $H_2O$ concentration. The sensitivity of the sensor is estimated to be about 2.5 Torr for pressure and 400 ppm for $H_2O$ concentration over a 3 cm absorption path length respectively. Accurate measurements for commercial freeze-dried products demonstrate the in-line applications of the sensor for the pharmaceutical industry.

## 1. Introduction

In today's aseptic manufacturing processes, automated leak detection and container closure integrity testing play an important role in protecting primary containers of finished product against microbial contamination [1,2]. The current growth in sterile biopharmaceutical products brings challenges as well as opportunities to the industry in terms of developing in-process monitoring and control strategies that keep processes in a state of control and minimize the risk of product defects [3]. For many finished sterile products, the most important destabilizing factor is the final residual moisture level in the vials of drugs [4,5]. There exist many traditional techniques and instruments for monitoring the moisture content in the vials, such as the residual gas analysis [6], the electronic hygrometer [7,8], the comparative pressure measurement [9], and the pressure rise measurement [10]. These techniques cannot give direct quantitative insight into the process. Instead, one has to establish the relationship between measurement and actual moisture content of the material *ex-situ* for different material and apparatus. Modern techniques such as the low temperature infrared spectroscopy [11], the visual microscopic observation [12], the low-resolution pulse nuclear magnetic resonance [13], and the X-ray powder diffractometry can give *in-situ* and non-destructive insight [14]. However, they are costly to maintain and difficult to validate.

Tunable diode laser absorption spectroscopy (TDLAS) is a rapid and non-destructive analytical method suitable for *in-situ* measurements of multiple parameters such as the concentration, pressure, temperature, and velocity in various environments [15–18]. The diode laser usually covers parts of the ro-vibrational bands of the relevant molecular species in the near-infrared or mid-infrared spectral regions. Semiconductor diode lasers are attractive sources for practical applications owing to their compactness, availability, robustness, compatibility with an optical fiber technology, and relatively ease of use. TDLAS have also been used to monitor gas parameters and vacuum levels in the headspace of sterile product containers in recent years. For example, For example, TDLAS has been demonstrated for the non-invasive determinations of the water pressure [19], the water vapor mass flow rate [20], the sublimation rate [21], the heat transfer parameters [22], and the oxygen concentration [23]. In order to reduce the influence of ambient gases, most of those systems need inert gas purges or sealed under vacuum. Additionally, reference vials with known concentration and pressure used for system calibration are also needed. All these additional features make system requirements more complicated and expensive. Headspace analyses are also performed based on TDLAS employing frequency modulation spectroscopy (FMS) [24–28]. The FMS scheme can yield a higher sensitivity, but disadvantages with regard to cost

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and system complexity must be considered. In addition, calibration with known gas is also needed for the FMS scheme. There are only very few sensors for headspace analyses are developed without purge system and calibration. For example, Jenkins et al. developed a diode laser absorption sensor for detecting oxygen concentration in headspace of vials employing a 760 nm Vertical Cavity Surface Emitting Laser and a balanced detection circuit. They performed an experiment to demonstrate the accuracy of the sensor using a cylindrical glass test tube to simulate a vial for pharmaceutical inspection applications, but did not confirm the ability of the sensor for commercial freeze-dried products and in-line applications of the sensor for the pharmaceutical industry [29]. To our knowledge, there has been no sensor capable of simultaneous measurement of headspace pressure and $H_2O$ concentration in closed vial employing direct absorption spectroscopy without inert gas purge system and calibration with known gas.

In the present paper, a sensor for simultaneous measurements of pressure and $H_2O$ vapor concentration in the headspace of vials using TDLAS with a distributed feedback (DFB) diode laser near 1.396 μm is developed. A $H_2O$ transition located near 7168.437 $\text{cm}^{-1}$ is selected for the sensor because of its strong absorption strength and isolation from interference of neighboring transitions. Due to the strong absorption of the $H_2O$ transition, the direct absorption scheme is employed for the sensor. This scheme is convenient for operation and good for the simplification of the system. Wavelength scans of the laser produced $H_2O$ direct absorption lineshapes for measurement path and reference path. The pressure and $H_2O$ vapor concentration in the headspace of vials are inferred from the difference between the measured signal and the referenced signal. In this way, the sensor does not need inert gas purges and calibration with known gas. Measurements are first validated in a static vial containing $H_2O$-Air mixtures over the expected pressure range of 0.01 to 1 atm. The sensitivity of the sensor is estimated through 20 successive pressure and concentration measurements recorded during a 20 min experiment time. In order to illustrate the potential of the sensor for in-line applications, measurements are performed on vials which are placed on a rotary stage to simulate the process of an assembly line. An experiment of headspace analysis for commercial freeze-dried products confirms the sensor's accuracy and potential utility for pharmaceutical industry.

## 2. Theory

The basic equation of absorption spectroscopy is the Beer–Lambert law [30]. This equation relates the transmitted intensity $I_t$ through a uniform gas medium of length $L$ [cm] to the incident intensity $I_0$ as

$$\left(\frac{I_t}{I_0}\right)_\nu = \exp[-k_\nu L] \tag{1}$$

where $k_\nu$ [$\text{cm}^{-1}$] is the spectral absorption coefficient. For an isolated transition $i$,

$$k_\nu = P x_{abs} S_i(T) \varphi_\nu \tag{2}$$

where $P$ [atm] is the total pressure, $x_{abs}$ is the mole fraction of the absorbing species, $S_i$ [$\text{cm}^{-2}\,\text{atm}^{-1}$] is the line strength at temperature $T$ [K] of the transition, and $\varphi_\nu$ [cm] is the line-shape function which is normalized such that $\int \varphi_\nu d\nu \equiv 1$. The product $k_\nu L$ is known as the spectral absorbance $\alpha_\nu$:

$$\alpha_\nu = -\ln\left(\frac{I_t}{I_0}\right) = k_\nu L = P x_{abs} S_i(T) \varphi_\nu L. \tag{3}$$

The measured absorbance from the target absorption transition is fitted with the appropriate line shape profile for the environmental conditions and the integrated absorbance is calculated from the fit. The integrated absorbance $A_i$ [$\text{cm}^{-1}$] could be expressed as

$$A_i = \int_{-\infty}^{+\infty} \alpha_\nu d\nu = P x_{abs} S_i(T) L = P_{abs} S_i(T) L \tag{4}$$

The integrated absorbance is directly proportional to species partial pressure $P_{abs}$ (and therefore concentration) at a fixed temperature.

The line-shape function $\varphi_\nu$ is usually approximated using a Voigt profile [31] characterized by the collision-broadened full-width at half maximum (FWHM), $\Delta\nu_C$ [$\text{cm}^{-1}$], and the Doppler FWHM, $\Delta\nu_D$ [$\text{cm}^{-1}$]. The collisional width $\Delta\nu_C$ is proportional to the system pressure in the following way:

$$\Delta\nu_C = P \sum_j x_j 2\gamma_{j-abs} \tag{5}$$

here, $\gamma_{j-abs}$ is the broadening coefficient due to collisions between perturbing species $j$ and the absorbing species.

In our case, the collisional FWHM from the Voigt profile can be written as

$$\Delta\nu_C = P_{air} 2\gamma_{air} + P_{H_2O} 2\gamma_{H_2O} \tag{6}$$

where $\gamma_{air}$ is the air-broadening coefficient of the transition and $\gamma_{H_2O}$ is the self-broadening coefficient of the sample. $P_{air}$ is the partial pressure of the perturber component (here laboratory air) and $P_{H_2O}$ is the partial pressure of water vapor.

$P_{air}$ and $P_{H_2O}$ can be obtained from Eqs. (4) and (6) if the temperature, line strength, and path length are known. Then we can obtain the mole fraction of water vapor, $x$, since

$$x_{H_2O} = P_{H_2O}/P = P_{H_2O}/(P_{air} + P_{H_2O}) \tag{7}$$

## 3. Experimental procedure

The experimental setup is shown in Fig. 1. The light source used is a single-mode InGaAsP DFB diode laser (NTT Electronics Corporation) operating in the near-infrared near 1.396 μm. The laser power is ~10 mW, and the typical linewidth is ~2 MHz. Frequency tuning of the diode laser could be controlled by scanning either the temperature (~0.43 $\text{cm}^{-1}$/°C) or the current (~0.02 $\text{cm}^{-1}$/mA). The temperature and current are controlled by ILX Lightwave LDX-3724B laser diode controller, with short-term (1 h) temperature stability $<0.004$ °C and long-term (24 h) temperature stability $<0.01$ °C. The calibration of the laser wavelength is made by a wavemeter (EXFO Burleigh Products Group, WA-1500-NIR) with an accuracy of about ±0.001 $\text{cm}^{-1}$. The laser wavelength is driven by a triangle ramp from a function generator (ShengPu, F-20). The optimum scanning frequency is limited by the re-triggering time of the DAQ hardware and is set as 333 Hz in the experiment.

The emitted radiation is collimated by a lens and divided in two beams by a 1 × 2 fiber splitter after passing through an optical isolator (Koncent, KISO-S-A-1550, −35 dB): as shown in Fig. 1, the first beam (~70% of the power) goes through the headspace of vial along its radial direction, while the second one (~30% of the power) passes through an open path in the ambient air. Both beams are then collected by two homemade InGaAs-PIN photodiodes. In order to minimize the difference between two detectors, the gain of the detectors were adjusted to yield almost the same voltages from the same light before experiment. In the experiment, the two signals are named as measured signal (from the first beam) and referenced signal (from the second beam) respectively. The detector used to acquire the referenced signal is fixed on a sliding guide and the length of the open path in the ambient air