Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 233 (2020) 118194

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Optimization of leakage detection system for vials based on two-line tunable diode laser absorption spectroscopy

Yuexing Zhang [a], Weiwei Wu [a], Huinan Yang [a,*], Chuanliang Li [b], Jin Tao [c], Ruifeng Kan [c]

[a] School of Energy and Power Engineering, Shanghai 200093, China
[b] Taiyuan University of Science and Technology, Taiyuan 030000, China
[c] The State Key Laboratory of Applied Optics, Changchun 130000, China

ARTICLE INFO

Article history:
Received 19 December 2019
Received in revised form 20 February 2020
Accepted 22 February 2020
Available online 24 February 2020

Keywords:
TDLAS
Measurement
Oxygen
Leakage
Vial

ABSTRACT

The leakage detection system of vials based on two-line water-vapor tunable diode laser absorption spectroscopy (TDLAS) developed in our previous work was first employed to investigate the instantaneous leakage processes of sealed vials. It showed that the leakage states of the vials with medicines cannot be accurately determined in a short time after the opening. Therefore, an optimized system was developed with two-line oxygen TDLAS method by the measurement of defined oxygen leakage coefficient, and it was then utilized to study the instantaneous leakage processes of sealed vials. It revealed that when the stoppers of the sealed vials were opened, the oxygen leakage coefficients increased immediately and then reach stable. It indicated that the optimized system was not affected by the water absorption of medicines. Furthermore, 15 vials with known leakage states were measured. It showed that the oxygen leakage coefficients of fully-open vials were obviously larger than that of sealed vials, and the maximum standard deviation of oxygen leakage coefficients for ten measurements of a single vial was 0.03%. The sealed vials with different leakage degrees were then investigated by inserting the needles with different sizes (0.5/1/2/3.5 mm) into the vials. It revealed that the time required for the oxygen leakage coefficients to reach stable was shorter for the vials with larger leakage degree, i.e., larger needle size inserted. It showed that non-invasive, fast response and high-accuracy leakage detection of vials can be realized by the optimized system.

1. Introduction

As shown in the analysis on the current situation and development of Chinese market, the number of vials required for the pharmaceutical industry reached about 50 billion in 2018. At present, vacuum method or nitrogen filled method are often applied in the pharmaceutical process to isolate the medicines in the vials from the ambient air, and the stability of medicines can be ensured. However, due to the cracks or untight assembly of the stoppers during the manufacturing and transportation process, the water vapor in the air easily enters into the vial, the medicines are deteriorated, the pesticide effects are reduced and the patients' lives can be endangered [1,2]. Therefore, the leakage detection of the vials is significant in pharmaceutical quality management and clinical medication safety.

The conventional leakage detection methods of vials (such as dye ingress method [3], microbial ingress method [4]) require visual observation of the color change, they are invasive and highly depended on artificial judgment. In recent years, the leakage states of vials have been investigated by many researchers based on laser absorption spectroscopy that is widely applied in the measurement of trace gases [5–12]. Jenkin et al. [13] measured the oxygen concentration in sealed vials based on tunable diode laser absorption spectroscopy (TDLAS). However, the measurement accuracy was affected by the etalon effect since the incident light was vertically transmitted into vials. Zhu et al. [14] effectively eliminated the etalon effect by adjusting the incident angle of the laser beam, and high-precision detection of the oxygen concentration in the vial can be achieved based on wavenumber modulation spectroscopy (WMS), but the system cannot meet the needs of industry due to relative slow detection speed (~5 s/vial). LIGHTHOUSE [15] provided benchtop headspace analyzers for leakage detection of the vials e.g., frequency modulation spectroscopy (FMS)-Oxygen headspace analyzer (FMS-760), FMS-Pressure/Moisture headspace analyzer (FMS-1400). With these products, the concentrations of corresponding gases (O_2, H_2O, etc.) inside the headspace of sealed vials can be determined, and the leakage states of the vials can be obtained. However, the measurement times required for each vial with these products are from 1 to 5 s. In our previous work, Wang et al. [16] proposed a three-lightpath water-vapor TDLAS method to realize leakage detection of vials. Chen et al. [17] developed a leakage detection system by

* Corresponding author.
E-mail address: yanghuinan@usst.edu.cn (H. Yang).

https://doi.org/10.1016/j.saa.2020.118194
1386-1425/

defining a leakage coefficient based on two-line water-vapor TDLAS method.

In this paper, the previous developed system [17] was first employed to measure the instantaneous leakage processes of sealed vials. However, it was found that the leakage states of the vials cannot be accurately determined. Therefore, an optimized system with two-line oxygen TDLAS method was developed. It revealed that the influence of water absorption of medicines on the measurement accuracy can be avoided, and the whole leakage processes can be tracked. The optimized system was then utilized to investigate 15 vials with known leakage states and vials with different leakage degrees.

2. Theory

For the optimized system, the two-line water-vapor TDLAS method [17] proposed in the previous work was improved. Fig. 1 is the measured signal as a function of time for a specific absorption line based on scanned-wavelength direct absorption spectroscopy. A third-order polynomial is fitted to the baseline region of the signal as shown by the dotted line, while the absorption spectrum can be obtained by subtracting the baseline. Two wavenumber positions (v_1 and v_2) are chosen, i.e., v_1 corresponds to strong absorbance and v_2 corresponds to no absorbance, and the leakage coefficient k can be then determined with the transmitted light intensities at v_1 and v_2.

As shown in Fig. 2, the absorption spectrum of oxygen, water vapor and carbon dioxide around 13,146.58 cm^{-1} were simulated under specific conditions ($x_{O2} = 0.2$, $x_{H2O} = 0.01$, $x_{CO2} = 0.0035$, $T = 298$ K, $P = 1$ atm, $L = 100$ cm) based on the high-resolution transmission (HITRAN) molecular absorption database 2016. It showed that there was strong absorption for oxygen, while there were almost no absorption for water vapor and carbon dioxide in this spectral region. It revealed that there was strong absorption of oxygen at 13,146.58 cm^{-1} and almost no absorption at 13,145.5 cm^{-1}, since the line strengths of oxygen at 13,146.58 cm^{-1} and 13,145.50 cm^{-2} were 7.137e−4 cm^{-2}/atm and 5.103e−8 cm^{-2}/atm, respectively. Therefore, these two wavenumber positions were chosen. The calculated absorbance of oxygen around 13,146.58 cm^{-1} at different pressures (0.1/0.2/0.3/0.4/0.5/0.6/0.7/0.8/0.9/1 atm) was shown in the Fig. 3. It was found that the absorbance almost kept constant when the pressure was larger than 0.3 atm, and it should be noted that the pressure in the sealed vials employed in the work provided by Zhejiang Medicine Company Limited were at ~0.45 atm. Therefore, the influence of pressure on the determination of leakage states is not considered here.

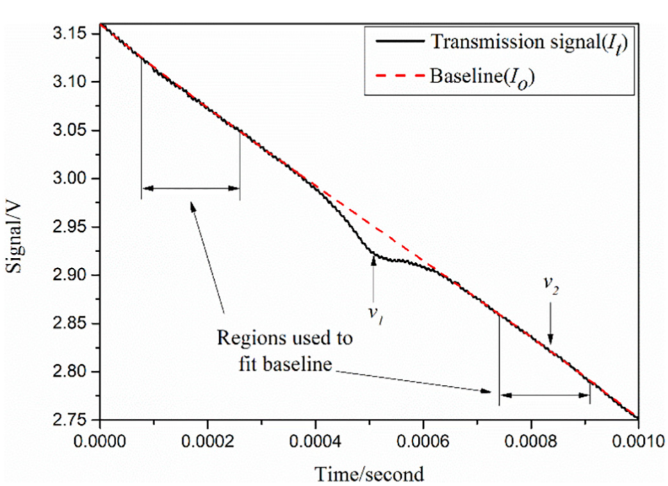

Fig. 1. Raw data and fit with scanned-wavelength direct absorption spectroscopy.

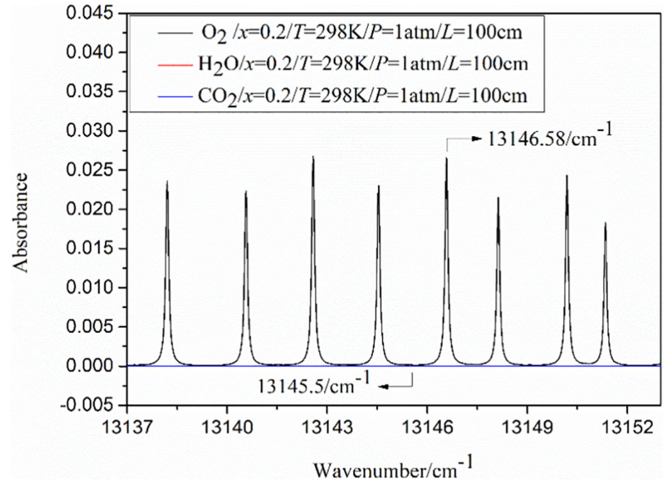

Fig. 2. Absorption spectrum of oxygen, water vapor and carbon dioxide around 13,146.58 cm^{-1}.

3. Results and discussion

3.1. Measurement of the instantaneous leakage processes of sealed vials based on two-line water-vapor tunable diode laser absorption spectroscopy

The previous developed two-line water-vapor TDLAS system [17] was firstly employed to investigate the instantaneous leakage process of sealed vials. The variations of leakage coefficient k with time for the vials with (a) and without (b) medicines before and after opening the stoppers were shown in Fig. 4. The experiments were performed at 298 K and relative humidity of 83%. As shown in Fig. 4a, the average value of k was about 0.0027 before opening the sealed vial with medicines, and k instantly raised to about 0.0147 after opening the stopper and then rapidly dropped to about 0.0032. As shown in Fig. 4b, the average value of k was about 0.0031 before opening the sealed vial without medicines, k immediately increased to about 0.0178 after opening the stopper and then tended to be stable. The deviation of k for each vial before opening the stopper could be caused by the different vacuum degrees. For the vial with medicines, it was found that the k first increased and then decreased after opening the stopper, i.e., the concentration of water vapor in the vial first increased and then decreased. Since the medicines were produced by low-temperature freeze-drying technology [18,19], they were provided with good

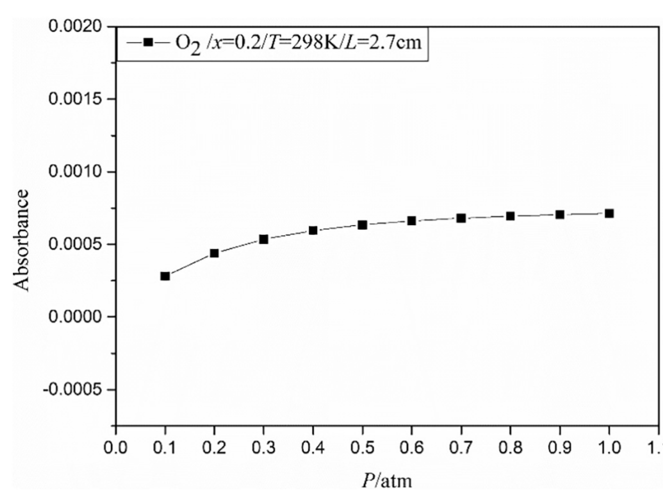

Fig. 3. Absorbance of oxygen at 13,146.58 cm^{-1} at different pressures.

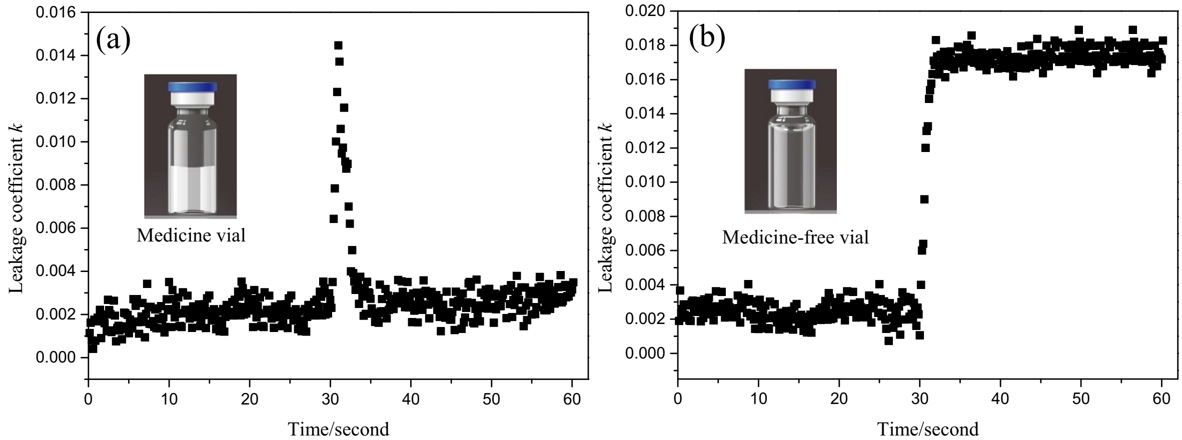

Fig. 4. Measurement of the instantaneous leakage processes of vials based on two-line water-vapor TDLAS.

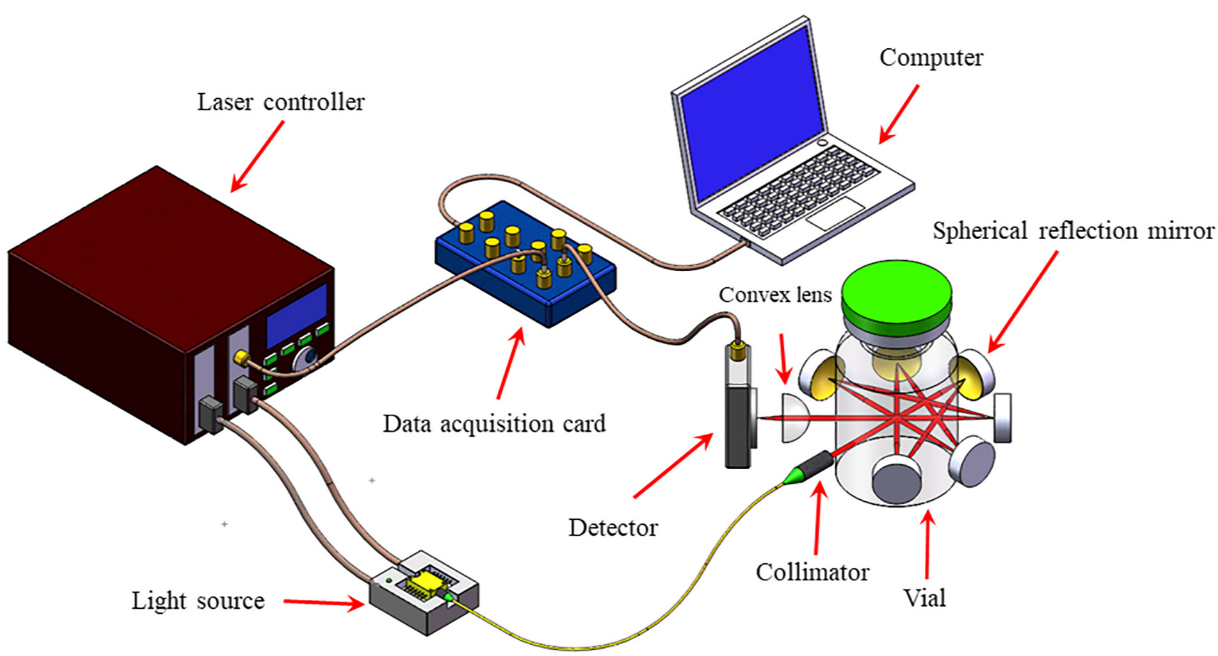

Fig. 5. The optimized system based on two-line oxygen TDLAS.

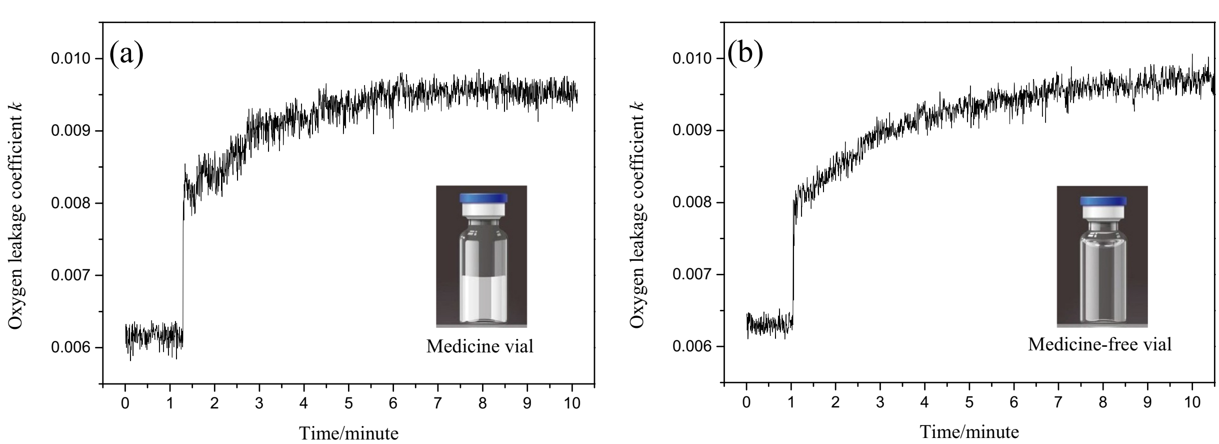

Fig. 6. Measurement of the instantaneous leakage processes of vials based on two-line oxygen TDLAS.

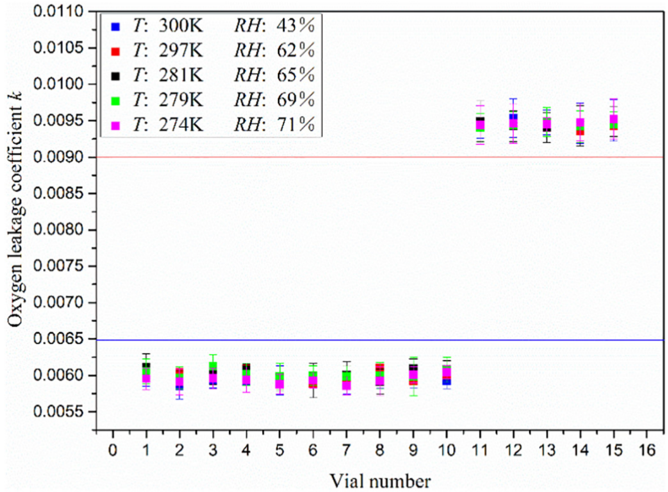

Fig. 7. *k* of 15 vials with known leakage states measured by the optimized system.

solubility and recovery ability of water absorption. The water vapor absorbed by the medicines when the water vapor in the air flowed into the vials. Therefore, it was found that when the vial was opened instantaneously, the leakage states of the vials after opening the vials in a short time cannot be accurately determined by this system. Since there is no oxygen absorption by the medicines, the leakage detection system was further optimized by measurement of oxygen.

3.2. The optimized system based on two-line oxygen tunable diode laser absorption spectroscopy

The schematic drawing of optimized system was shown in Fig. 5. A 761 nm distributed feedback (DFB) diode laser (Nanoplus, NP-DFB-761-SM-BTF) was butterfly mounted and chosen as the light source. Its output power is 2.6 mW, and its temperature- and current-tuning coefficients were 0.05 nm/ °C and 0.021 nm/mA, respectively. The operating temperature and current of the laser were set by the laser controller (Thorlabs, PRO8000) as 22.15 °C and 30 mA, respectively, the center wavelength of laser output can be then ensured at 13,146.58 cm^{-1}. Saw-tooth signal with repetition rate of 1000 Hz was employed to tune the laser. 150 consecutive scans were averaged and smooth filtered. Based on the simulation calculation by HITRAN 2016 ($T = 298$ K, $P = 1$ atm, $L = 2.7$ cm (the diameter of the vials), $x_{O2} = 0.2$), the absorbance of oxygen at 13145.8 cm^{-1} was only 7.1e-4. It revealed that high-accuracy measurement cannot be achieved with the limited path length. Therefore, the path length of the optimized system was increased by optical design. The laser beams were reflected by six gold-coated spherical mirrors (Edmund, 43-340), and the path length was then increased to ~40 cm. The light was finally received by the detector (Thorlabs, PDA10CS). The incident light entered the vial with an incident angle of 5° from the horizontal plane to effective eliminate the etalon effect. The signal was converted and transferred to the computer with the data acquisition card (NI, USB6361). The acquisition and processing of the experimental data were performed in the LabVIEW environment. Measurement time of three vials with the optimized system was 1 s, it was much faster than the LIGHTHOUSE products.

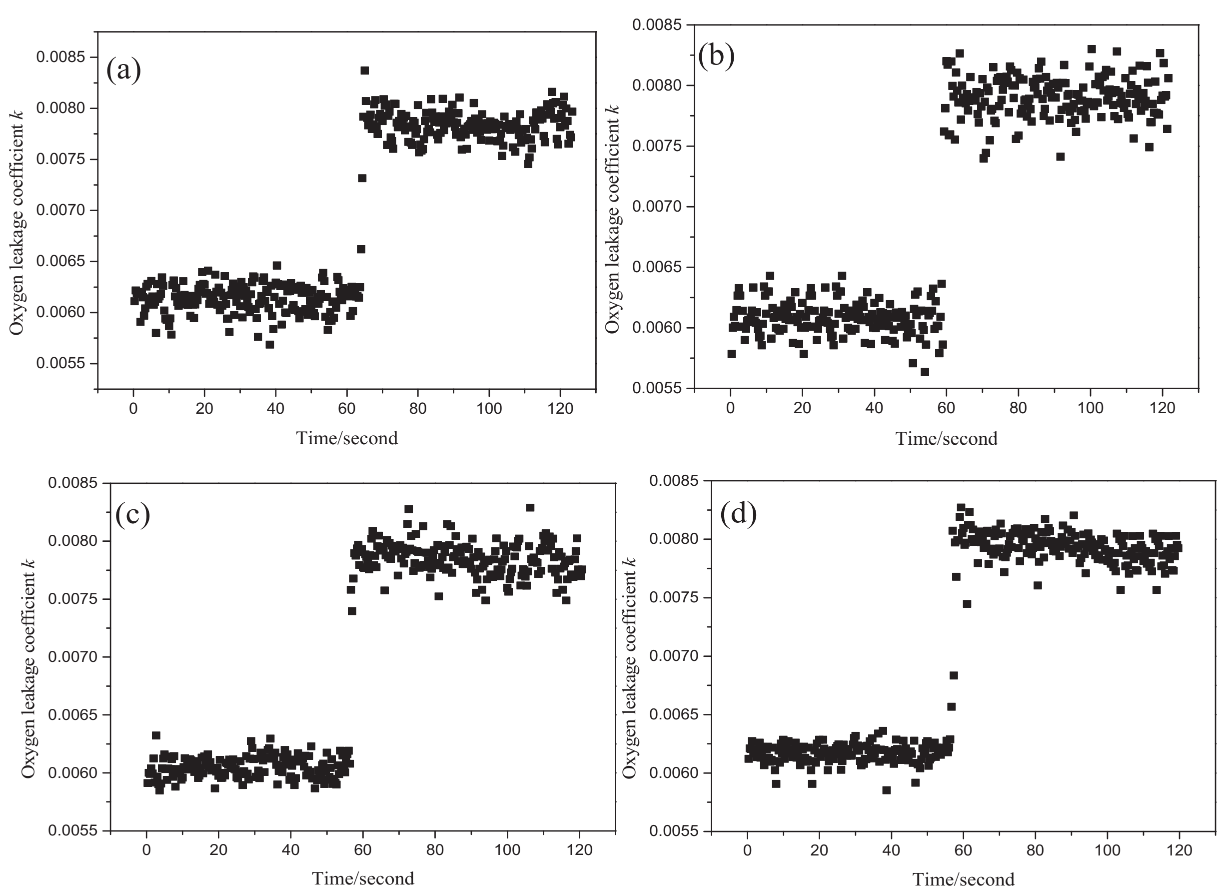

Fig. 8. The variations of *k* within 2 min after insertion of needles with different sizes into vials (a) 0.5 mm; (b) 1 mm; (c) 2 mm; (d) 3.5 mm.

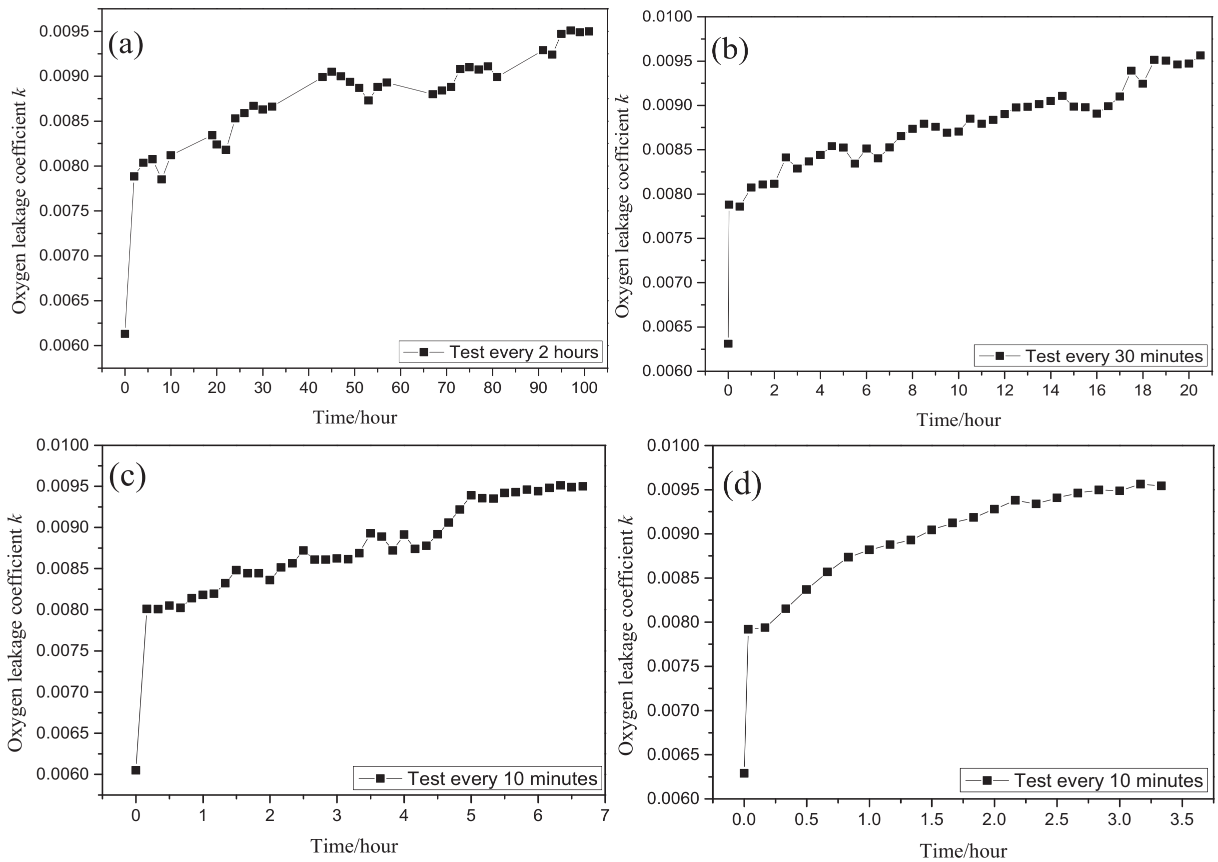

Fig. 9. The variations of *k* with time after insertion of needles with different sizes into vials (a) 0.5 mm; (b) 1 mm; (c) 2 mm; (d) 3.5 mm until *k* reached stable.

3.3. Investigation on the instantaneous leakage processes of vials by the optimized system

The optimized system was utilized to investigate the instantaneous leakage processes of sealed vials. The variations of *k* with time for the vials with (a) and without (b) medicines before and after opening the stoppers for 10 min were shown in Fig. 6. As shown in Fig. 6a, the average value of *k* was about 0.00628 before opening the sealed vial with medicine, and *k* rapidly raised to about 0.008 after opening the stopper, gradually increased to about 0.0095 and then reached stable. As shown in Fig. 6b, the average value of *k* was about 0.00633 before opening the sealed vial without medicine, and *k* immediately raised to about 0.008 after opening the stopper, gradually increased to about 0.0095 and then reached stable. It was found that the optimized system was not affected by the water absorption of medicines, and the entire leakage processes of vials can be tracked.

3.4. Measurement of 15 vials with known leakage states by the optimized system

15 vials with known leakage states were randomly placed ten times and measured by the optimized system, i.e., No. 1–10 vials were sealed and No. 11–15 vials were fully open. They were placed in the ambient air for 24 h before the measurements. The experiments were performed at different temperatures (294–300 K) and relative humidities (43%–71%). As shown in Fig. 7, *k* of No. 1–10 vials were less than 0.0065, and *k* of No. 11–15 vials were greater than 0.0090. It revealed that the oxygen leakage coefficients of fully-open vials were obviously larger than that of sealed vials. The deviation of *k* for each vial can be caused by the various vacuum degrees, and the maximum standard deviation for ten measurements of a single vial was 0.03%. It showed that there was obvious interval to separate the sealed and fully-open vials, temperature and humidity in the environment will not influence on the measurement accuracy.

3.5. Measurement of vials with different leakage degrees by the optimized system

In order to investigate the vials with different leakage degrees, four needles with different sizes (0.5/1/2/3.5 mm) were inserted into four sealed vials. The variations of *k* with time for these four vials before and after insertion within 2 min were shown in Fig. 8. It revealed that the average value of *k* before insertion for one-minute continuous measurement of these four vials were 0.00613/0.00628/0.00609/0.00631, respectively. When the needle was inserted into the vial, the air in the environment quickly entered the vial due to the pressure difference inside and outside of the vial. The pressure inside the vial instantly increased until it was equal to the atmospheric pressure. After 1 min, the average value of *k* of these four vials was 0.00791/0.00793/0.008/0.00801, respectively. Fig. 9 showed the variations of *k* with time before and after insertion until *k* reached stable for these four vials, and the temporal resolution of the measurement were 2 h/30 min/10 min/10 min, respectively. Since the oxygen in the environment entered into the vial through the needle by molecular diffusion after the insertion, the oxygen concentration in the vial reached equilibrium with the environment finally. It was found that the *k* gradually increased, and the time required for reaching equilibrium for these four vials were 95/20/6/3.3 h, respectively. It indicated that the required time was shorter for the vial with larger needle size.

4. Conclusion

Since the instantaneous leakage states of sealed vials with medicines cannot be accurately determined by the water-vapor TDLAS system, the two-line oxygen TDLAS system was developed in the work. It revealed that the optimized system was not affected by the water absorption of medicines in the vials, and the whole leakage processes of vials can be tracked. 15 vials with known leakage states were investigated. It shown that k of fully-open vials was greater than 0.0090, while k of sealed vials was less than 0.0065. Furthermore, the vials with different leakage degrees were also studied. It indicated that the times required for k to reach stable were 95/20/6/3.3 h for different needles sizes 0.5/1/2/3.5 mm, respectively. It shown that the leakage states of the vials can be determined by the optimized system without interference, and it can be widely applied in major hospitals and pharmaceutical industry in the future.

CRediT authorship contribution statement

Yuexing Zhang: Methodology, Writing - original draft.**Weiwei Wu:** Investigation, Data curation.**Huinan Yang:**Conceptualization, Writing - review & editing, Supervision.**Chuanliang Li:**Software.**Jin Tao:**Validation.**Ruifeng Kan:**Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by National Natural Science Foundation of China (NSFC) (Grant Nos. 51676130, 51776129, U1810129) and State Key Laboratory of Applied Optics Open Fund (SKLAO-201909).

References

[1] A.N. Zacher, M.H. Zornow, G. Evans, Drug contamination from opening glass ampules, Anesthesiology 75 (5) (1991) 893–895.
[2] G.X. Li, R.Q. Zheng, Oxidative deterioration of drugs and its prevention, J. Chinese Journal of Nature. 4 (1988) 36–38.
[3] S.B. Lana, W.C. Mary, E.D. George, J.L. Willam, Development of a dye ingress method to assess container-closure integrity: correlation to microbial ingress, PDA Journal of Pharmaceutical Science and Technology 54 (6) (September 2000) 449–455.
[4] S. Rizwan, S. Robert, S. Mark, Y. Pk, Microbial ingress through breaches in aseptic manufacturing systems: experimental investigation of pressure-driven leaks of liquids, PDA J. Pharm. Sci. Technol. 61 (3) (September 2007) 154–159.
[5] H.N. Yang, D. Greszik, T. Dreier, C. Schulz, Simultaneous measurement of liquid water film thickness and vapor temperature using near-infrared tunable diode laser spectroscopy, J. Applied Physics B-Lasers and Optics. 99 (3) (2010) 385–390.
[6] T. Cai, G. Wang, Z. Cao, W. Zhang, X. Gao, Sensor for headspace pressure and H_2O concentration measurements in closed vials by tunable diode laser absorption spectroscopy, J. Optics and Lasers in Engineering. 58 (04) (2014) 48–53.
[7] M.A. Bolshow, Y.A. Kuritsyn, Y.V. Romanovskii, Tunable diode laser spectroscopy as a technique for combustion diagnostics, J. Spectrochimica Acta Part B-Atomic Spectroscopy. 106 (2014) 45–66.
[8] P. Werle, F. Slemr, K. Maurer, R. Kormann, R. Mücke, B. Jänker, Near-and mid-infrared laser-optical sensors for gas analysis, J. Optics And Lasers in Engineering. 37 (23) (2002) 101–114.
[9] S. Neethu, R. Verma, S.S. Kamble, J.K. Radhakrishnan, P.P. Krishnapur, V.C. Padaki, Validation of wavelength modulation spectroscopy techniques for oxygen concentration measurement, J. Sensors and Actuators B-Chemical. 192 (2014) 70–76.
[10] T. Svensson, M. Lewander, S. Svanberg, Laser absorption spectroscopy of water vapor confined in nanoporous alumina: wall collision line broadening and gas diffusion dynamics, Opt. Express 18 (16) (2010), 16460.
[11] R. Sur, K. Sun, J.B. Jeffries, J.G. Socha, R.K. Hanson, Scanned-wavelength-modulation-spectroscopy sensor for CO, CO_2, CH_4 and H_2O in a high-pressure engineering-scale transport-reactor coal gasifier, Fuel 150 (2015) 102–111.
[12] X.Q. Guo, F. Zheng, C.L. Li, Q.S. He, A portable sensor for in-situ measurement of ammonia based on near-infrared laser absorption spectroscopy, Opt. Lasers Eng. 51 (3) (2019) 243–248.
[13] T.P. Jenkins, T. Berg, Diode laser absorption sensor for detecting oxygen in head space of vials, IEEE Sensors, 2008.
[14] G.F. Zhu, X. Hu, H.Q. Zhu, E.Z. Hu, J.P. Zhu, The multi-beam interference suppression for measuring penicillin vial's oxygen concentration based on tunable diode laser absorption spectroscopy, J. Spectroscopy and Spectral Analysis. 38 (2) (2018) 372–376.
[15] http://www.lighthouseinstruments.com/index.php?pid=30&lang=en.
[16] M. Wang, W.G. Dai, H.N. Yang, J. Chen, M.X. Su, X.S. Cai, Leakage detection of vials based on TDLAS, Laser & Optoelectronics Progress 54 (8) (2017) 337–343.
[17] H.N. Yang, J.J. Chen, X. Luo, D. Qi, X. Xin, M. Su, Leakage detection of closed vials based on two-line water vapor TDL AS, J. Measurement. 135 (2019) 413–417.
[18] A. Hottot, S. Vessot, J. Andrieu, Freeze drying of pharmaceuticals in vials: influence of freezing protocol and sample configuration on ice morphology and freeze-dried cake texture, Chem. Eng. Process. Process Intensif. 46 (7) (2007) 666–674.
[19] X.C. Wang, Z.F. Wu, Y.H. Li, Y.K. Xiong, M. Yang, Application status and prospect of low temperature drying technology in traditional Chinese medicine, J. Chinese Journal of Pharmaceuticals. 50 (1) (2019) 42–47.