Frequency modulation spectroscopy

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Frequency modulation spectroscopy (FMS) is opening up exciting new applications using diode lasers in process spectroscopy.

Diode lasers have found several applications in process monitoring. They are low cost, have narrow line widths and are well suited for high-resolution spectroscopy. For these reasons, most applications have been in gas monitoring over medium to long pathlengths. The high specificity offered by the ability to measure individual rotational bands has been useful for both atmospheric trace gas analysis and process gas analysis, typically emissions monitoring. Lead salt lasers are available as sources for the mid-infrared region, but require cooling to liquid nitrogen temperatures, while near infrared diodes (based on III–V semiconductors) operate at room temperature and are commercially available. However, the relative weakness of absorption of NIR overtones has tended to limit applications to long pathlength measurements.

The wavelength of diode lasers may be tuned by temperature and/or current control, with the range depending on the individual laser materials and structure. Tuning the wavelength offers the opportunity both to scan the laser through an absorbance line and also to apply a high frequency modulation to shift the detection bandwidth to high frequency where laser intensity noise is reduced towards the shot noise limit and subsequently the signal-to-noise ratio is increased by several orders of magnitude. The concept is analogous to the way voice, video and data information are encoded in the side bands of a radio transmission carrier wave.

A diode laser is frequency modulated by superimposing a radio frequency oscillation, Ω, onto the diode injection current. The spectral output of a radio frequency modulated diode laser, shown at the top of Figure 1, consists of a carrier frequency ω_c and side band frequencies, $\omega_c \pm \Omega$. When the laser frequency is then tuned through an absorption band, the amount of light absorbed, which by Beer's Law is proportional to the gas concentration, is "written" into the side band frequencies. This is shown schematically as a decrease in the amplitude of the upper side band ($\omega_c \pm \Omega$) at the top of Figure 1. The absorption information is extracted using phase-sensitive detection techniques. A mixer demodulates the radio frequency signal and outputs a voltage proportional to gas concentration. The demodulated absorption feature is shown in Figure 2, note that the FMS output is the derivative of the absorbance band. The gas concentration is proportional to the peak-to-peak amplitude of the FM signal.

So now we have a spectroscopic technique which has good sensitivity for specific gases over relatively short pathlengths. Diode lasers are available at frequencies which are suitable to measure several gases which have absorbances in the NIR, including water and oxygen. (Oxygen has an electric dipole forbidden absorbance band between 760 and 766 nm with P and R branch rotational fine structure.)

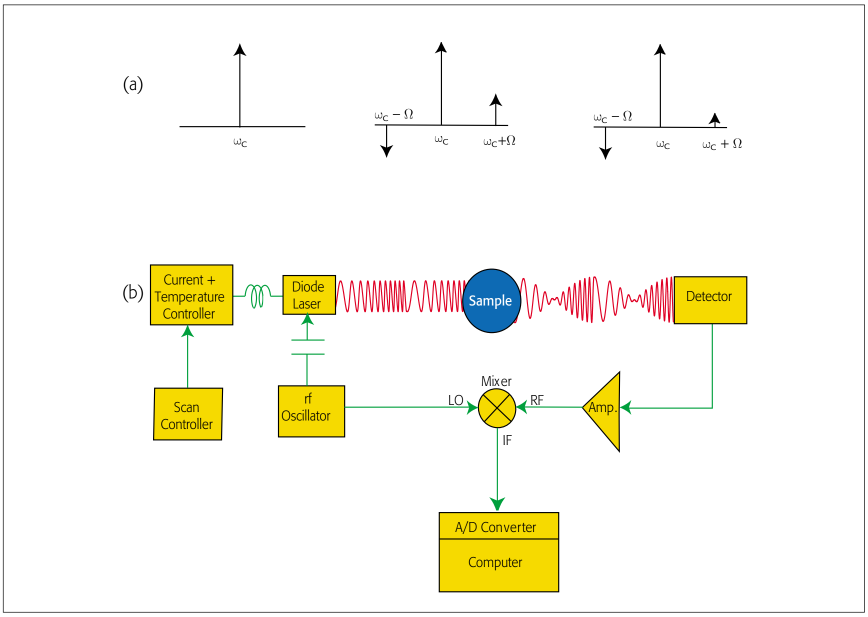

Figure 1. (a) Frequency and intensity profile of a diode laser beam: unmodulated, modulated with no absorption and modulated with absorption. (b) Schematic diagram of the frequency modulation spectroscopy technique. The frequency modulated diode laser output is converted to an amplitude modulation after passing through a gas sample which absorbs at a particular wavelength. The amplitude modulation is proportional to gas concentration and can be phase sensitively detected.

Applications of FMS

FMS has found several applications in the pharmaceutical industry as a headspace analysis tool. With the growth of biotechnology a growing proportion of the products from the industry are parenterals: drugs designed to be administered intravenously or by injection. Typically these are liquids (or freeze dried solids) packaged in glass or plastic vials, and are manufactured under aseptic conditions. They are packaged under an inert nitrogen atmosphere or under vacuum to prevent oxidative degradation and it is important to know if oxygen has been excluded from the package and whether air can enter the vials through cracks or problems with stoppers. The US FDA has recently produced a draft guidance document which states: *"A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to nonsterility. Equipment suitability problems or incoming container or closure deficiencies have caused loss of container closure system integrity. As examples, failure to detect vials fractured by faulty machinery, or by mishandling of bulk finished stock, has led to drug recalls. If damage that is not readily detected leads to loss of container closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects."*[1] There are two ways in which FMS can help meet this requirement: oxygen measurements or pressure measurements.

As shown above, oxygen concentration can be measured by FMS. An instrument calibration constant, k, is determined using a vial filled with a certified gas mixture of 20% oxygen and 80% nitrogen. When the 20% oxygen reference standard is inserted to the instrument, the system response (signal amplitude, *S*, and power, *P*) is measured and stored. The instrument records the measured signal and detected laser power, then using the known amount of oxygen computes a calibration constant k,

$$k = (P / S) \times \%\ \text{oxygen}$$

where *P* is the detected laser power, *S* is the peak-to-peak absorption signal (see Figure 2) and % oxygen is the concentration in the calibration vial. The measured values of *P* and *S* are typically the result of 1000 averaged high frequency scans, collected in less than 2 s. A commercial instrument has been developed for laboratory and on-line analysis. Ingress of air into packages is readily detected by monitoring oxygen content.

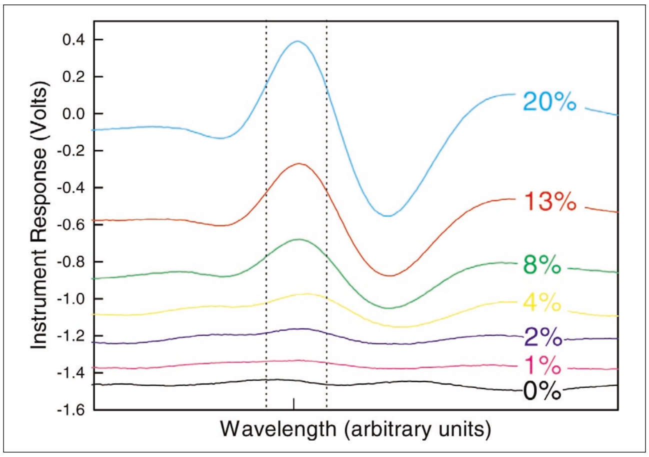

Figure 2. Frequency modulation signals from oxygen absorption. The peak-to-peak amplitude of each spectrum is proportional to oxygen concentration (noted to the right of each scan). These spectra were taken through 1″ diameter glass containers filled with certified gas mixtures of oxygen in nitrogen.

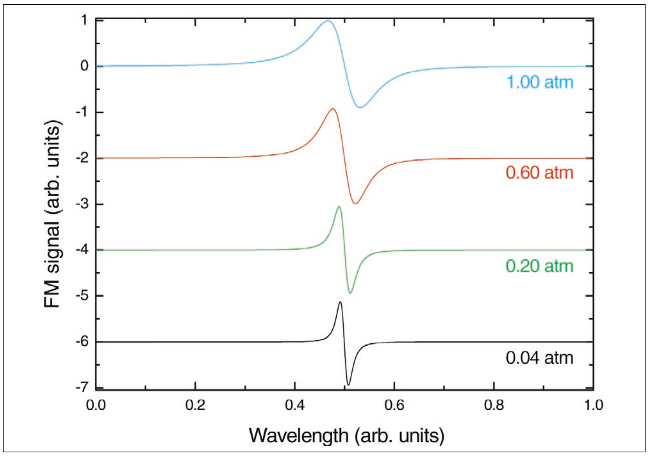

Figure 3. Water band width for vials with different headspace pressures.

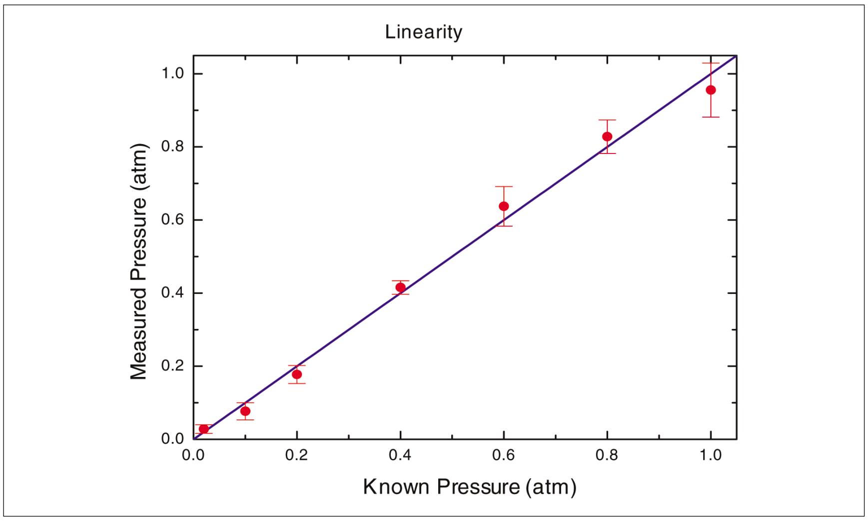

Figure 4. Calibration curve using standards of known pressure. The instrument responds linearly to pressure over the range 0.04 atm to 1.0 atm.

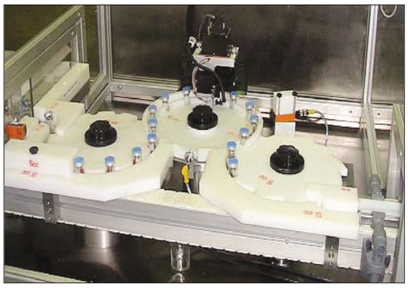

Figure 5. Commercial FMS spectrometer for 100% inspection of headspace pressure in sealed vials capable of measuring 100s of vials per day (courtesy of Lighthouse Instruments Inc.).

Because the instrument is working in the NIR, glass and most plastic packages are suitable candidates for measurement.

Pressure in a sealed container may be monitored spectroscopically by measuring the width of a single water absorbance. The broadening of the width of a gas-phase rotational absorption line is largely due to a combination of collision broadening and Doppler broadening, therefore the width of the FMS absorption signal is proportional to total headspace pressure. Figure 3 shows a water band response for a set of four calibration standards at known pressures, showing how the FMS signal width varies with total pressure.

The speed of FMS (sub-second measurement times) lends itself to on-line measurement of parenteral containers in real time. The non-invasive, non-destructive nature of the FMS measurement is ideal for 100% inspection of containers which can contain expensive product and where the only alternative is destructive sampling of random samples from the batch. Commercial instruments have been developed, installed and validated to measure the pressure in thousands of vials per day using FMS technology (Figure 5).

So, a relatively new spectroscopic technique has found applications within pharmaceutical production processes worldwide. Another Process Spectroscopy success story!

Further reading

1. *Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice*. www.fda.gov/cder/guidance/1874dft.htm
2. I. Linnerud, P. Kaspersen, T. Jaeger, "Gas monitoring in the process industry using diode laser spectroscopy", *Appl. Phys. B* **67**, 297–305 (1998).
3. J.A. Silver, "Frequency-modulation spectroscopy for trace species detection: theory and comparison among experimental methods", *Appl. Optics* **31**, 707–717 (1992).
4. J. Veale, *Non-Destructive Headspace Gas Analysers*. Technical Note, Lighthouse Instruments Inc., Charlottesville, VA, USA.