



INDEX OF REFRACTION (IOR) TECHNOLOGY FOR CONCENTRATION MONITORING IN BIOPHARMACEUTICAL MANUFACTURING

Introduction

Most biopharmaceutical products and processes, from the most basic applications to the highly complex, require advanced process analytical techniques (PAT). Processes ranging from media and buffer preparation to chromatography and sanitization require liquid chemical concentration and temperature monitoring to optimize and ensure process performance. Errors in chemical concentration at any process step can result in loss of high-value product, reduced product quality/efficacy and reduction in productivity. For this reason, quality control of liquid chemicals is essential and requires reliable, precise, easy to use analytical instrumentation with fast response time.

Currently, there are many methods used to measure chemical concentration including refractive index, conductivity, pH and osmolality. This technical note will introduce a refractive index technology, which provides a direct measurement of concentration. This measurement is most closely related to the dielectric constant of a fluid or mixture, and it typically varies linearly with density.¹ The note will then discuss three indirect measurement methodologies: conductivity, pH and osmolality – all of which face limitations of dynamic range, linearity, precision, limits of detection (LOD) and limits of quantification (LOQ).²

Index of Refraction Measurement

Refractive index or index of refraction (IoR) is a unit of measurement describing how light bends when passing from one medium into another. Combined with Snell's Law, which is a formula that describes the relationship between the angle of incidence and the angle of refraction, index of refraction can be used in biopharmaceutical manufacturing to provide a direct measure of the concentration of solutions.

Unlike traditional refractometry, which operates in a transmission-type geometry, this IoR technology utilizes a miniaturized optical sensor in a reflection-type geometry. In the traditional transmission mode, light travels through the fluid, whereas in reflection mode, light reflects off the back side of an optical window in contact with the solution. Utilizing reflection geometry eliminates the challenges associated with turbidity, diffraction and absorption.



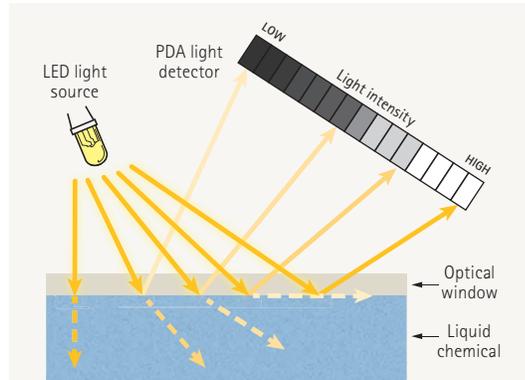
The miniaturized sensor offers scalable, fast, accurate and reliable monitoring of your buffer and CIP chemicals.

How Entegris' IoR Technology Works

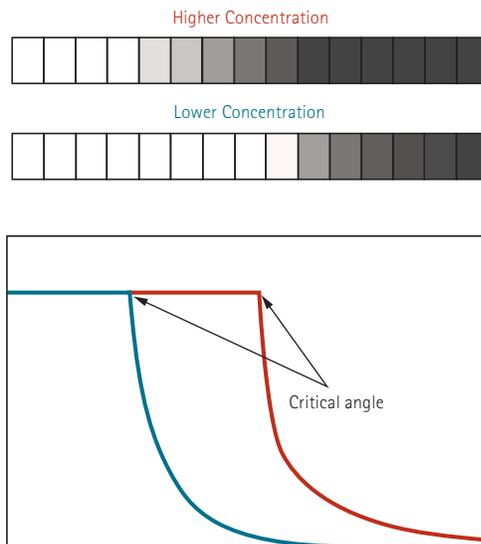
Utilizing the miniaturized optical sensor, a light emitting diode (LED) shines light onto an optical window, which is in contact with the liquid being measured. Light from the LED reflects off the optical window into a photodiode array (PDA) detector, and the critical angle (θ_c) is measured where light is refracted into the fluid and not reflected back to the PDA detector. The index

of refraction of the liquid is determined³ from equation 1, where n_b is the refractive index of the sample, and n_a is the refractive index of the refractometer optics. Concentration is then determined by calibrating the IoR to the liquid's concentration.

$$\sin(\theta_c) = \frac{n_b}{n_a}$$



As the liquid concentration changes, so does θ_c . The IoR technology measures these changes in θ_c quickly (100 milliseconds) and accurately (better than ± 0.2 wt%). Using internal averaging of the 100 millisecond data rate to increase resolution, it reports an IoR (or concentration) every 1 second. Additionally, because IoR depends on the temperature of the liquid, a thermistor is used to monitor the temperature and automatically compensate the IoR (and thereby the concentration) of the liquid in real time.



Indirect Methodologies — Reviewing Conductivity, pH and Osmolality

Conductivity is a measurement of a solution's ability to conduct electricity. This method can work well for highly ionic solutions but is limited in its ability to measure nonionic chemistries. Because of this nonionic limitation and the fact that the critical constituents of many buffers and nutrient media are weakly ionic and non-ionic, IoR will offer a measurement that provides a stronger correlation to product quality.⁴

pH measures the acidity or basicity of an aqueous solution. This measurement method has limited capability in solvent-based liquids or where dissociation does not result in the production of hydronium ions. Due to the fact that a pH measurement depends on the electronic properties of a solution, IoR can provide a more consistently accurate option for concentration monitoring.

Osmolality is the measure of solute concentration and is defined as the number of osmoles per liter of solution. A limiting factor for osmolality in terms of concentration monitoring is accuracy, typically 0.1 wt%. Another major limitation is that, unlike the other technologies, this is an off-line measurement which requires sampling and does not provide real time process measurement.

IoR Technology Solves Common Measurement Challenges

The effects of errors in chemical concentration can range from minimally impactful to entire batch loss. Concentration monitoring technology that can meet the challenges of accuracy, timing or speed of data availability, and the ability to perform across a broad range of solutions ensures quality at virtually any process step.

Entegris' IoR technology provides real-time, accurate, repeatable concentration and temperature measurements for in-line and off-line monitoring of process liquids. Providing fast and accurate performance, this technology offers response times as fast as 100 milliseconds and better than ± 0.2 wt% (100 ppm) accuracy in most applications.

To meet footprint challenges, the miniaturized optical sensor allows for agile packaging and interface to any in situ process while maintaining performance. It also provides packaging flexibility to meet benchtop and flow-through needs at any process step. For use in multiple applications— from cell culture and fermentation to separation, chromatography and bulk fill—this IoR technology can be implemented as a replacement technology for existing concentration monitoring or as an additional quality control measure to those already in place.

While there are highly valid uses for conductivity, pH and osmolality in biopharmaceutical manufacturing, the IoR technology brings a higher level of accuracy and repeatability to a broader range of chemicals. Its small footprint provides the ability to monitor at virtually any point in the process, while its packaging flexibility performs from lab to full-scale production. For in-line process requirements, this IoR technology provides information in real time, allowing for fast response to process variations. Additionally, this technology is non-invasive, eliminating the risk of drug substance contamination.⁵

References

1. Liu, Y. and Daum, P., “*Relationship of refractive index to mass density and self-consistency of mixing rules for multicomponent mixtures like ambient aerosols*,” *Journal of Aerosol Science*, June 6, 2008, www.sciencedirect.com, accessed on June 13, 2014.
2. Schreiber, B., Wacinski, C. and Chiarello, Dr. R., “*Index of Refraction as a Quality Control Metric for Liquids in Pharmaceutical Manufacturing*,” *Pharmaceutical Engineering*, 2013. Print.
3. Halliday, D. and Resnick, R., *Fundamentals of Physics*, John Wiley and Sons, New York, 1981, pp 693.
4. Tison, S., “*A New Innovation in Chemical Measurement*,” *Production Insight*, VWR International, October 2014.
5. Schreiber, B., Wacinski, C. and Chiarello, Dr. R., op. cit.

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