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⟨831⟩ REFRACTIVE INDEX

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▲INTRODUCTION

Refractive index is a basic physical property of pharmaceutical materials. This general chapter only applies to the measurement of liquid pharmaceuticals, solutions, solvents, and liquid raw materials with stand-alone instruments and not to detectors of chromatographic systems. Refractive index measurements of liquid pharmaceuticals, solutions, solvents, and liquid raw materials are useful for the following:

- Identifying a pure substance
- Establishing the purity of some substances
- Determining the concentrations of some solutions such as alcohol solutions or sugar solutions (e.g., percentage of sugar in syrup)
- Determining the uniformity of final compounded preparations

The refractive index (n) of a substance, or medium, is defined as:

$$n = \frac{c}{v}$$

where c is the velocity of light in a vacuum and v is the velocity of light in the medium. For example, the refractive index of pure water at a measurement temperature and wavelength of 20° and 589 nm is 1.3330, meaning that light travels proportionately slower in water than in a vacuum.¹ The refractive index of a material is dependent on the temperature and the wavelength of light used to measure it; it is important to have precise control of both of these variables to accurately measure the refractive index. Refractive index is reported as n_{λ}^T , where T is the temperature, and λ is the wavelength of the incident beam (in nanometers). For example, the refractive index of water at 20° using the sodium D-line (at 589 nm) may be reported as either n_{589}^{20} or $n_D^{20} = 1.3330$.¹

QUALIFICATION OF REFRACTOMETERS

Qualification of refractometers can be divided into three elements: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). For further discussion, see [Analytical Instrument Qualification \(1058\)](#).

Installation Qualification

The IQ requirements provide evidence that the hardware and software are properly installed in the desired location.

Operational Qualification

The OQ for the refractometer should verify the temperature control of the sample and the accuracy and repeatability of the refractive index measurements. The apparatus should provide refractive index readings to ± 0.0001 , and it should provide a means of operation at the prescribed temperature, with readings accurate to at least $\pm 0.1^\circ$. The certified reference materials used must have an equal or better expanded uncertainty than ± 0.001 . Prior to verifying the operation of the refractometer, perform a full calibration of the instrument as instructed by the manufacturer.

ACCURACY

Verify the accuracy of the refractometer by measurement of certified reference materials that bracket the operational range of the instrument. The result should agree with the stated certified value within the limits of the expanded uncertainty of the reference material added to the accuracy specification of the instrument (as provided by the manufacturer). Additional uncertainty components may be included, according to the manufacturer's recommendation.

REPEATABILITY

Verify the repeatability of the refractometer by measuring at least two different certified reference materials covering the intended operational range of the instrument. Perform at least six replicate measurements of each certified reference material. The result should be equal to or less than the stated repeatability performance specification of the instrument (as provided by the manufacturer).

Performance Qualification

PQ includes two stages: periodic instrument calibration and performance evaluation. Instrument calibration should be performed periodically according to the instrument manufacturer's instructions. The second stage of PQ evaluation should be conducted at regular intervals or on day of use by verifying the refractive index of suitable reference materials.

PROCEDURES**Sample Preparation**

Samples should be kept in well-closed containers to protect them from any changes in composition due to differences in temperature and/or relative humidity at different locations. If the sample to be evaluated is not homogenous, is hazy, or is known to contain suspended particles or an emulsified phase—factors that influence the measurement—the sample should be clarified by filtration or centrifugation prior to measurement.

Measurement Procedure

Determine the refractive index of the sample per the instrument manufacturer's instructions. Unless otherwise indicated in the monograph, the refractive index is measured at 25°, with reference to the wavelength of the sodium D-line (at 589 nm).¹▲ (USP 1-Dec-2023)

¹ The sodium D-line is identified as a doublet at 589.0 and 589.6 nm with a center wavelength at 589.3 nm in air.

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

| Topic/Question | Contact | Expert Committee |
|------------------------|---|--|
| <831> REFRACTIVE INDEX | Yang Liu Manager, Product Quality and Analytical Methods | GCPA2020 General Chapters - Physical Analysis 2020 |

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