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⟨781⟩ OPTICAL ROTATION

CHANGE TO READ:

INTRODUCTION

Many pharmaceutical substances are optically active in the sense that they rotate an incident plane of polarized light so that the transmitted light emerges at a measurable angle to the plane of the incident light. This property is characteristic of some crystals and of many pharmaceutical liquids or solutions of solids. Where the property is possessed by a liquid or by a solute in solution, it is generally the result of the presence of one or more asymmetric centers, usually a carbon atom with four different substituents. The number of optical isomers is 2^n, where *n* is the number of asymmetric centers. Polarimetry, the measurement of optical rotation, of a pharmaceutical substance may be the only convenient means for distinguishing optically active isomers from each other and thus is an important criterion of identity and purity.

Substances that may show optical rotatory properties are “chiral”. Those that rotate light in a clockwise direction are “dextrorotatory” or “(+) optical isomers”, and those that rotate light in a counterclockwise direction are called “levorotatory” or “(−) optical isomers”. (The symbols *d*- and *l*-, formerly used to indicate dextrorotatory and levorotatory isomers, are no longer sanctioned owing to confusion with D- and L-, which refer to configuration relative to D-glyceraldehyde. The symbols *R* and *S*, or α and β, are also used to indicate configuration, the arrangement of atoms or groups of atoms in space.)

The physicochemical properties of nonsuperimposable chiral substances rotating plane-polarized light in opposite directions to the same extent, “enantiomers”, are identical, except for this property and in their reactions with other chiral substances. Enantiomers often exhibit profound differences in pharmacology and toxicology, owing to the fact that biological receptors and enzymes themselves are chiral. Many pharmaceutical substances from natural sources, such as amino acids, proteins, alkaloids, antibiotics, glycosides, and sugars, exist as chiral compounds. Synthesis of such compounds from nonchiral materials usually results in equal amounts of the enantiomers, i.e., “racemates”. Racemates have a net null optical rotation, and their physical properties may differ from those of the component enantiomers. ▲▲ (USP 1-Dec-2024) Stereoselective or stereospecific synthetic methods or separation of racemic mixtures can be used to obtain individual optical isomers.

Measurement of optical rotation is performed using a polarimeter. For a neat, undiluted liquid, the specific rotation is a function of the density of the liquid at the temperature of interest:

$$[\alpha]_\lambda^t = \frac{\alpha}{l\rho}$$

When measuring the specific rotation of an analyte in solution, it may be convenient to prepare the *Sample solution* in a volume containing a mass of the analyte, with a concentration of the analyte per unit of volume (g analyte/mL solution), c_v, or per unit of mass (g analyte/g solution), c_w. The equations for determining the specific rotation of a *Sample solution* are:

For *Sample solution* (g/mL):

$$[\alpha]_\lambda^t = \frac{\alpha}{lc_v}$$

For *Sample solution* (g/g):

$$[\alpha]_\lambda^t = \frac{\alpha}{l\rho c_w}$$

$[\alpha]_\lambda^t$ = specific rotation at wavelength λ and temperature *t* (°C). The units of specific rotation are $[(^\circ) \cdot mL \cdot dm^{-1} \cdot g^{-1}]$, which is typically expressed just as degrees (°).

α = observed rotation in degrees (°)

l = path length (dm)

ρ = density of the solution or liquid at temperature *t* (g/mL)

c_v = concentration of the analyte per unit of volume (g analyte/mL solution)

c_w = concentration of the analyte per unit of mass (g analyte/g solution)

For some pharmaceutical substances, especially liquids such as essential oils, the optical rotation requirement is expressed in terms of the observed angle of optical rotation, α, measured under conditions defined in the monograph.

Historically, polarimetry was performed using an instrument where the extent of optical rotation is estimated by visual matching of the intensity of split fields. For this reason, the D line of the sodium lamp at the visible wavelength of 589 nm was most often employed.[1]

Specific rotation determined at the D line at 25° C or 20° C is expressed by the symbol:

$$[\alpha]_D^{25} \text{ or } [\alpha]_D^{20}$$

Much of the data available are expressed in this form. Use of lower wavelengths, such as those available with the mercury lamp lines isolated by means of filters of maximum transmittance at approximately 546, 436, 405, and 365 nm in a photoelectric polarimeter, has been found to provide advantages in sensitivity with a consequent reduction in the concentration of the test compound. In general, the observed optical rotation at 436 nm is about double, and at 365 nm, about 3 times that at 589 nm.[1]

It is now common practice to use other light sources such as light emitting diodes (LEDs) or xenon or tungsten halogen lamps, with appropriate filters, instead of traditional light sources because these contemporary light sources may offer advantages of cost, long life, and broad wavelength emission range.

Change to read:

QUALIFICATION OF POLARIMETERS

Qualification of polarimeters can be divided into three elements: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). For a more detailed discussion, see *Analytical Instrument Qualification* ⟨1058⟩.

Installation Qualification (IQ)

The IQ requirements provide evidence that the hardware and software are properly installed in the desired location and ambient conditions (temperature and humidity).

Operational Qualification (OQ)

The OQ for the polarimeter should verify the temperature control of the sample, the wavelength accuracy and bandwidth of the light source, the accuracy and repeatability of the optical rotation measurements at the operating wavelengths, and for quantitative applications, the linearity of the instrument response.

TEMPERATURE CONTROL

The optical rotation is affected by the temperature of the sample. Therefore, proper temperature control of the sample will be critical for maintaining suitable accuracy and repeatability of the optical rotation measurements. The polarimeter should report the temperature of measurement to at least ±0.1° C or better and should be capable of maintaining constant temperature during the measurement. The OQ of a polarimeter's temperature control is performed by demonstrating that the operating temperature is within ±0.5° C of a temperature recorded on a temperature reading device that is traceable to a National Institute of Standards and Technology (NIST) standard or equivalent (see *General Notices, 6.80.30 Temperature Reading Devices*).

WAVELENGTH ACCURACY AND BANDWIDTH

For polarimeters that employ continuum light sources (e.g., LED or tungsten halogen lamps), bandpass filters are typically used to select the wavelength for measurement. It is recommended to record attributes of the wavelength and the bandwidth ▲(i.e., the wavelength characteristics of the bandpass filter used in the instrument).▲ (USP 1-Dec-2024) If other light sources are employed (e.g., sodium emission lamps), it is recommended to record the wavelength.

ACCURACY OF OPTICAL ROTATION

To verify accuracy of the polarimeter, the polarimeter must be capable of reporting the optical rotation to ±0.01° or better, and the certified optical rotation reference material must be certified to ±0.01° or better. Verify the accuracy of the polarimeter at the operating wavelength(s) by measuring a certified optical rotation reference material having an associated expanded uncertainty. Typically, quartz plate reference standards with certified optical rotation values are used.[2] Alternatively, other suitable certified reference materials or reference standards may be used.[3] 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).

REPEATABILITY

Perform at least five replicate measurements of a reference material at the operating wavelength. ▲Typically, the same reference standard or certified reference material used in *Accuracy of Optical Rotation* is used to assess repeatability. Calculate the variability of the replicates, typically expressed as standard deviation.▲ (USP 1-Dec-2024) The result should be equal to or less than the stated repeatability performance specification of the instrument (as provided by the manufacturer).

LINEARITY

Linearity should be verified if the optical rotation measurement is used for quantitation of an enantiomer. For quantitative applications, linearity is verified if ▲▲ (USP 1-Dec-2024) three or more ▲optical rotation ▲ (USP 1-Dec-2024) values representing the operational range meet the criteria for accuracy.

Performance Qualification (PQ)

PQ consists of periodic qualification of optical rotation accuracy and repeatability as well as temperature control, along with performance checks performed as needed by the instrument user.

PROCEDURES

When polarimetry is used to differentiate an optically active material (e.g., a pure chiral isomer) from an optically inactive material (e.g., a racemic mixture of substances), the polarimeter may provide a small, measurable optical rotation that is close to 0°, which may require interpretation to determine whether the result indicates that a material is classified as dextrorotatory, levorotatory, or optically inactive. The term "dextrorotatory" should be interpreted to mean that the observed angle of optical rotation is a positive, optically active value of optical rotation. The term "levorotatory" should be interpreted to mean that the observed angle of optical rotation is a negative, optically active value of optical rotation. The term "optically inactive" should be interpreted to mean the observed angle of rotation is not significantly different from 0°.

For a neat, undiluted liquid, follow the procedure for *Angular Rotation* in this chapter unless otherwise indicated in the monograph. (In some cases, a drug product is treated as a neat, undiluted liquid.) For *Test solutions* or *Sample solutions* prepared by diluting the analyte in a solvent, follow the procedure for *Specific Rotation* in this chapter unless otherwise indicated in the monograph.

Temperature, which applies to the solution or the liquid under test, should be maintained to ±0.5° C of the stated value.

Specific Rotation

The reference "⟨781S⟩" in a monograph signifies that specific rotation is to be calculated from observed optical rotations in the *Test solution* or *Sample solution* obtained as directed therein. Unless otherwise directed, measurements of optical rotation are made in a 1.0-dm measurement cell at 589 nm at 25° C ± 0.5° C corrected for the reading of the solvent blank.[1] Unless otherwise specified, specific rotation is calculated on the dried basis where *Loss on Drying* ⟨731⟩ is specified in the monograph or on the anhydrous basis where *Water Determination* ⟨921⟩ is specified.

Optical rotation of solutions should be determined within 30 min of preparation. In the case of substances known to undergo racemization or mutarotation, care should be taken to standardize the time between adding the solute to the solvent and introduction of the solution into the polarimeter measurement cell.

Angular Rotation

The reference "⟨781A⟩" in a monograph signifies, unless otherwise directed, that the optical rotation of the neat, undiluted liquid is measured in a 1.0-dm measurement cell at 589 nm at 25° C ± 0.5° C corrected for the reading of the dry, empty measurement cell blank.[1] The result is reported as the observed angle of optical rotation.

[1] All references of wavelengths are in vacuum. The sodium D line is 589.44 nm in vacuum and 589.3 nm in air.

[2] Qualification may be performed using a polarization reference standard, which consists of a plate of quartz mounted in a holder perpendicular to the light path. Acceptable periodic calibrations may be made by a National Metrology Institute (NMI) that is signatory to the International Committee for Weights and Measures Mutual Recognition Arrangement (CIPM MRA) or an ISO/IEC 17025 accredited laboratory for calibration where the accreditation body is a signatory to the International Laboratory Accreditation Cooperation Mutual Recognition Arrangement (ILAC MRA).

[3] A certified reference material is available from the Office of Standard Reference Materials, National Institute of Standards and Technology (NIST), Gaithersburg, MD 20899, as a current lot of Standard Reference Material, Sucrose.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<781> OPTICAL ROTATION	Yang Liu Manager, Product Quality and Analytical Methods	GCPA2020 General Chapters - Physical Analysis 2020

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