

(781) OPTICAL ROTATION

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 article 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 power are *chiral*. Those that rotate light in a clockwise direction as viewed towards the light source are *dextrorotatory*, or (+) *optical isomers*. Those that rotate light in the opposite direction are called *levorotatory* or (–) optical isomers. (The symbols *d*- and *l*-, formerly used to indicate dextro- 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* and 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 articles from natural sources, such as amino acids, proteins, alkaloids, antibiotics, glycosides, and sugars, exist as chiral compounds. Synthesis of such compounds from nonchiral materials results in equal numbers of the enantiomers, *racemates*. Racemates have a net null optical rotation, and their physical properties may differ from those of the component enantiomers. Use of 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.* The general equation used in polarimetry is:

$$[\alpha]_t^c = \frac{100a}{lc}$$

where $[\alpha]$ is the specific rotation at wavelength λ , t is the temperature, a is the observed rotation in degrees ($^\circ$), l is the pathlength in decimeters, and c is the concentration of the analyte in g per 100 mL. Thus, $[\alpha]$ is 100 times the measured value, in degrees ($^\circ$), for a solution containing 1 g in 100 mL, measured in a cell having a pathlength of 1.0 dm under defined conditions of incident wavelength of light and temperature. For some Pharmacopeial articles, especially

*Suitable calibrators are available from the Office of Standard Reference Materials, National Institute of Standards and Technology (NIST), Gaithersburg, MD 20899, as current lots of Standard Reference Materials, Dextrose and Sucrose. Alternatively, calibration may be checked using a Polarization Reference Standard, which consists of a plate of quartz mounted in a holder perpendicular to the light path. These standards are available, traceable to NIST, from Rudolph Research Analytical, 354 Route 206, Flanders, NJ 07836, or from Rudolph Instruments, Inc., 40 Pier Lane, Fairfield, NJ 07004-2113.

liquids such as essential oils, the optical rotation requirement is expressed in terms of the observed rotation, a , 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. Specific rotation determined at the D-line is expressed by the symbol:

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

and 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 578, 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 three times that at 589 nm. Reduction in the concentration of the solute required for measurement may sometimes be accomplished by conversion of the substance under test to one that has a significantly higher optical rotation. Optical rotation is also affected by the solvent used for the measurement, and this is always specified.

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

Change to read:

Specific Rotation—The reference *Specific Rotation* (781S) in a monograph signifies that specific rotation is to be calculated from observed optical rotations in the *Test solution* \blacktriangle or *Sample solution* \blacktriangle_{USP35} obtained as directed therein. Unless otherwise directed, measurements of optical rotation are made at 589 nm at 25 $^\circ$. Where a photoelectric polarimeter is used, a single measurement, corrected for the solvent blank, is made. Where a visual polarimeter is employed, the average of no fewer than five determinations, corrected for the reading of the same tube with a solvent blank, is used. Temperature, which applies to the solution or the liquid under test, should be maintained within 0.5 $^\circ$ of the stated value. Use the same cell for sample and blank. Maintain the same angular orientation of the cell in each reading. Place the cell so that the light passes through it in the same direction each time. Unless otherwise specified, specific rotation is calculated on the dried basis where *Loss on Drying* is specified in the monograph, or on the anhydrous basis where *Water* is specified.

Optical rotation of solutions should be determined within 30 minutes 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 tube.

Angular Rotation—The reference *Angular Rotation* (781A) in a monograph signifies, unless otherwise directed, that the optical rotation of the neat liquid is measured in a 1.0-dm tube at 589 nm at 25 $^\circ$, corrected for the reading of the dry empty tube.

<785> OSMOLALITY AND OSMOLARITY

INTRODUCTION

Osmotic pressure plays a critical role in all biological processes that involve diffusion of solutes or transfer of fluids through membranes. Osmosis occurs when solvent but not solute molecules cross a semipermeable membrane from regions of lower to higher concentrations to produce equilibrium. The knowledge of osmotic pressures is important for practitioners in determining whether a parenteral solution is hypo-osmotic, iso-osmotic, or hyperosmotic. A quantitative measure of osmotic pressure facilitates the dilution required to render a solution iso-osmotic relative to whole blood.

OSMOTIC PRESSURE

The osmotic pressure of a solution depends on the number of particles in solution, and is therefore referred to as a colligative property. A particle can be a molecule or an ion or an aggregated species (e.g., a dimer) that can exist discretely in solution. A solution exhibits ideal behavior when no interaction occurs between solutes and solvent, except where solvent molecules are bound to solutes by hydrogen bonding or coordinate covalency. For such a solution containing a nondissociating solute, the osmotic pressure (π) is directly proportional to its molality (number of moles of solute per kilogram of the solvent):

$$\pi = (\rho RT/1000)m,$$

where ρ is the density of the solvent at the temperature T (in the absolute scale); R is the universal gas constant; and m is the molality of the solution. For a real solution containing more than one solute, the osmotic pressure is given by the formula:

$$\pi = (\rho RT/1000)\sum v_i m_i \Phi_{m,i}$$

where v_i is the number of particles formed by the dissociation of one molecule of the i^{th} solute; $v_i = 1$ for nonionic (nondissociating) solutes; m_i is the molality of the i^{th} solute; and $\Phi_{m,i}$ is the molal osmotic coefficient of the i^{th} solute. The molal osmotic coefficient takes into account the deviation of a solution from ideal behavior. Its value depends upon the concentration of the solute(s) in solution, its chemical properties, and ionic characteristics. The value of the molal osmotic coefficient of a solute can be determined experimentally by measuring the freezing point depression at different molal concentrations. At concentrations of pharmaceutical interest, the value of the molal osmotic coefficient is less than one. The molal osmotic coefficient decreases with the increase in concentration of the solute (Table 1).

OSMOLALITY

The osmolality of a solution ξ_m is given by

$$\xi_m = \sum v_i m_i \Phi_{m,i}$$

The osmolality of a real solution corresponds to the molality of an ideal solution containing nondissociating solutes and is expressed in osmoles or milliosmoles per kilogram of solvent (Osmol per kg or mOsmol per kg, respectively), a unit that is similar to the molality of the solution. Thus, osmolality is a measure of the osmotic pressure exerted by a real solution

across a semipermeable membrane. Like osmotic pressure, other colligative properties of a solution, such as vapor pressure lowering, boiling point elevation, and freezing point depression, are also directly related to the osmolality of the solution. Indeed, the osmolality of a solution is typically determined most accurately and conveniently by measuring freezing point depression (ΔT_f):

$$\Delta T_f = k_f \xi_m$$

where k_f is the molal cryoscopic constant, which is a property of the solvent. For water, the value of k_f is 1.860° per Osmol. That is, 1 Osmol of a solute added to 1 kg of water lowers the freezing point by 1.860°.

OSMOLARITY

Osmolarity of a solution is a theoretical quantity expressed in osmoles per L (Osmol per L) of a solution and is widely used in clinical practice because it expresses osmoles as a function of volume. Osmolarity cannot be measured but is calculated theoretically from the experimentally measured value of osmolality.

Sometimes, osmolarity (ξ_c) is calculated theoretically from the molar concentrations:

$$\xi_c = \sum v_i c_i$$

where v_i is as defined above, and c_i is the molar concentration of the i^{th} solute in solution. For example, the osmolarity of a solution prepared by dissolving 1 g of vancomycin in 100 mL of 0.9% sodium chloride solution can be calculated as follows:

$$[3 \times 10 \text{ g/L}/1449.25(\text{mol. wt. of vancomycin}) + 2 \times 9 \text{ g/L}/58.44(\text{mol. wt. of sodium chloride})] \times 1000 = 329 \text{ mOsmol/L}$$

The results suggest that the solution is slightly hyperosmotic because the osmolality of blood ranges between 285 and 310 mOsmol per kg. However, the solution is found to be hypo-osmotic and has an experimentally determined osmolality of 255 mOsmol per kg.¹ The example illustrates that osmolarity values calculated theoretically from the concentration of a solution should be interpreted cautiously and may not represent the osmotic properties of infusion solutions.

The discrepancy between theoretical (osmolarity) and experimental (osmolality) results is, in part, due to the fact that osmotic pressure is related to osmolality and not osmolarity. More significantly, the discrepancy between experimental results and the theoretical calculation is due to the fact that the osmotic pressure of a real solution is less than that of an ideal solution because of interactions between solute molecules or between solute and solvent molecules in a solution. Such interactions reduce the pressure exerted by solute molecules on a semipermeable membrane, reducing experimental values of osmolality compared to theoretical values. This difference is related to the molal osmotic coefficient ($\Phi_{m,i}$). The example also illustrates the importance of determining the osmolality of a solution experimentally, rather than calculating the value theoretically.

MEASUREMENT OF OSMOLALITY

The osmolality of a solution is commonly determined by the measurement of the freezing point depression of the solution.

Apparatus—The apparatus, an osmometer for freezing point depression measurement, consists of the following: a means of cooling the container used for the measurement; a

¹Kastango, E.S. and Hadaway, L. *International Journal of Pharmaceutical Compounding* 5, (2001) 465-469.