

Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

2.4.9. Conductivity

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This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

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Change to:

2.4.9. Conductivity

This General Chapter has been harmonized with corresponding texts of the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopoeia.

Portions of the IP text that and are not part of the PDG harmonized text, are marked with symbols (♦♦).

The current I (in amperes) flowing in a conductor is directly proportional to the applied electromotive force E (in volts) and inversely proportional to the resistance R (in ohms) of the conductor.

$$I = \frac{E}{R}$$

The conductivity of a solution (K) is the reciprocal of resistivity (ρ) which is defined as the quotient of the electric field and the density of the current (flowing in the conducting solution). The resistance R (in Ω) of a conductor of cross section S (in cm^2) and length L (in cm) is given by the expression $R = \rho \times L/S$ or $1/K \times L/S$; thus, $K = 1/R \times L/S$ where, L/S corresponds to the ideal cell constant.

The unit of conductivity in the International System is the siemens per metre (S m^{-1}). What is generally used in expressing the electrical conductivity of a solution is siemens per centimetre (S cm^{-1}) or microsiemens per centimetre ($\mu\text{S cm}^{-1}$). The resistivity of a solution is expressed in ohm centimetres ($\Omega \text{ cm}$).

Unless otherwise stated, the reference temperature for the expression of conductivity or resistivity is 25°.

This general chapter provides information on how to apply electrical conductivity measurements (hereafter referred to as 'conductivity') of fluids, including pure liquids. This chapter is intended for ♦other♦ fluid applications when conductivity is used to measure, monitor or control chemical dispensing (e.g. chemical purity or ionic concentration), and other applications where the ionic character of the fluid needs to be known or controlled.

Applications include, but are not limited to, solutions that may be used in clean-in-place, chromatography detection, ionic solution preparation, end point detection, dosing, fermentation and buffer production. In some cases, conductivity measurements can be extended to pure organic fluids such as alcohols and glycols where a weak conductivity signal exists, and the signal can be significantly increased if the organics become contaminated with water or salts.

Conductivity is the measurement of the ability of a fluid to conduct electricity via its chemical ions. The ability of any ion to electrically conduct is directly related to its ion mobility. Conductivity is directly proportional to the concentrations of ions in the fluid according to Equation 1:

$$\kappa = 1000 \sum_i^{\text{all ions}} C_i \lambda_i$$

κ = conductivity (S/cm)

C_i = concentration of chemical ion i (mol/l)

λ_i = specific molar conductance of ion i ($\text{S} \cdot \text{cm}^2/\text{mol}$)

Although the SI unit S/m is the appropriate SI unit for conductivity, historically the unit S/cm has been selected by industry as the accepted unit.

On the basis of Equation 1, conductivity is not ion selective because it responds to all ions. Furthermore, the specific molar conductance of each ion is different. As a result, unless the percentage composition of ions of the solution is limited and known, the precise concentrations of ionic species cannot be determined from conductivity measurements. However, for examples such as a solution of a single salt or acid or base, such as a caustic solution used in cleaning, the precise concentration can be directly determined. Despite the lack of ionic specificity, conductivity is a valuable laboratory and process tool for measurement and control of total ionic content because it is proportional to the sum of the concentrations of all ionic species (anions and cations) for diluted solutions as described in Equation 1. At higher concentrations, conductivity measurements are not perfectly linear with concentration. Conductivity measurements cannot be applied to solids or gases, but they can be applied to the condensate of gases.

Another variable that influences conductivity measurements is the fluid temperature. As the fluid temperature increases, the ion conductance increases, making this physicochemical phenomenon the predominant reason for the temperature-compensation requirement when testing conductive fluids.

The conductivity, κ , is proportional to the conductance, G (S), of a fluid between two electrodes (Equation 2):

$$\kappa = G \times \left(\frac{d}{A}\right) = G \times K$$

κ = conductivity (S/cm)

G = conductance (S)

d = distance between the electrodes (cm)

A = area of the conducting electrodes (cm²)

K = cell constant (cm⁻¹), which also equals the ratio of d/A

The resistivity ρ (Ω -cm) of the fluid is, by definition, the reciprocal of the conductivity (Equation 3):

$$\rho = 1/\kappa = 1/(G \times K) = R/K$$

ρ = resistivity (Ω -cm)

κ = conductivity (S/cm)

G = conductance (S)

K = cell constant (cm⁻¹)

R = resistance (Ω), which is the reciprocal of the conductance, G

Apparatus. The apparatus used is a conductivity meter that measures the resistance of the column of liquid between the electrodes of the immersed conductivity cell (the measuring device). The meter is supplied with alternating current and is equipped with a temperature probe and a temperature compensation device. The generally used conductivity cell contains two parallel platinum electrodes coated with platinum black, each with a surface area S , and separated from the other by a distance L . The electrodes are protected by a glass tube. Other types of cells may also be used.

An electrical conductivity measurement consists of the determination of resistance of the fluid between and around the electrodes of the conductivity sensor. To achieve this measurement, the primary instrumentation is the resistance-measuring circuit and the conductivity sensor, and they are usually connected by a cable when the sensor and the user interface are separated.

The resistance measurement is made by applying an alternating current (AC, meaning the flow of electric charge periodically reverses direction) voltage (or current) to the electrodes, measuring the current (or voltage), and calculating the resistance according to Ohm's law. The alternating source is used to prevent the polarization (collection of ions) at the electrodes. Depending on the instrument, the measuring frequency of the measuring system adjusts automatically according to the measuring conditions of the instrument, and there may be multiple resistance-measuring circuits embedded in the measuring system. The resistance-measurement circuit may be embedded in the transmitter or in the sensor.

The conductivity sensor consists of at least two electrical conductors of a fixed size and geometry, separated by an electrical insulator. The electrodes, insulator, and any other wetted materials should be constructed of materials that are unreactive to fluids with which they may come into contact. Also, the sensor construction should withstand the environmental conditions (process or ambient temperature, pressure, cleaning applications) that it would be subjected to.

Most conductivity sensors have temperature devices such as a platinum resistance temperature device (RTD) or negative temperature coefficient (NTC) thermistor embedded inside the sensor, although external temperature

measurement is possible. The purpose of the temperature measurement is for temperature compensation of the conductivity measurement.

Procedure

Determination of the cell constant. Use a certified reference material (such as a solution of potassium chloride) with conductivity less than 1500 S cm^{-1} and the cell constant shall be within 2 per cent of the given value. A high cell constant is necessary when solutions of high conductivity are tested. Commonly used conductivity cells have cell constants of the order of 0.1 cm^{-1} , 1 cm^{-1} and 10 cm^{-1} .

Use a certified reference material (such as a solution of potassium chloride) with a conductivity value near the expected value of the solution under examination. Rinse the cell several times with *distilled water* and at least twice with the certified reference material used for the determination of the cell constant of the conductivity cell. Measure the resistance of the conductivity cell using the certified reference material at $25 \pm 1^\circ$. The cell constant is given by the expression $K = R_{\text{CRM}} \times K_{\text{CRM}}$, where, R_{CRM} is the measured resistance in mega ohms and K_{CRM} is the conductivity of the certified reference material solution used, in microsiemens per centimetre.

NOTE—Other certified reference materials may be used especially for cells having a constant of 0.1 cm^{-1} .

The measured constant K of the conductivity cell must be within 5 per cent of the value indicated.

If the cell constant is determined at a temperature other than that indicated for the certified reference material, the conductivity value is calculated from the expression:

$$K_t = K_{\text{CRM}} \times [1 + \alpha (T - T_{\text{CRM}})]$$

where, K_t = value of conductivity at the different temperature,

K_{CRM} = value of conductivity of the certified reference material,

T = temperature set for calibration,

T_{CRM} = temperature indicated for the certified reference material,

α = temperature coefficient for the conductivity value of the certified reference material (0.021 for potassium chloride).

Cell Constant Determination

The purpose of the sensor's cell constant is to normalize the conductance (or resistance) measurement for the geometrical construction of the two electrodes.

The cell constant is determined by immersing the conductivity sensor in a solution of known conductivity. Solutions of known conductivity can be obtained by preparation of specific mixtures according to national authoritative sources or procurement of commercially available certified and traceable standard solutions. These recipes or certified solutions can range from 5 to 200,000 $\mu\text{S/cm}$, depending on the level of accuracy desired. Alternatively the cell constant is determined by comparison to other reference conductivity measuring systems (also available as an accredited calibration service). *[NOTE—Conductivity measurements are not perfectly linear with concentration.]*

The measured cell constant of the conductivity sensor must be within 5 per cent of the nominal value indicated by the sensor certificate, unless otherwise prescribed.

Modern conductivity sensors normally do not change their cell constant over their lifetime. If a change of the cell constant is detected during calibration, a cleaning of the sensor is appropriate according to the manufacturer's recommendations. Following that, the calibration procedure should be repeated. Sometimes "memory effects" appear, particularly when changing from high to low concentrations if the sensor is not well flushed.

Calibration of meter. Calibration can be done by replacing the conductivity cell with officially certified precision resistors (accurate to ± 0.1 per cent of the stated value) or an equally accurate adjustable resistance device to give a predicted instrument response. Each scale on the meter may have to be calibrated prior to use. The instrument must have a minimum resolution of $0.1 \mu\text{S cm}^{-1}$.

Method. After the apparatus has been calibrated with a certified reference material solution, rinse the conductivity cell several times with *distilled water* and at least twice with the aqueous solution under examination. Carry out successive measurements as described in the individual monograph.

Calibration of Temperature

In addition to verifying the sensor's cell constant, the embedded temperature device (or external temperature device) should be appropriately calibrated for the application to apply the temperature compensation algorithm accurately. The temperature accuracy that is required depends on the criticality of the temperature to the application. An accuracy of $\pm 1^\circ$ typically suffices.

Calibration of Measurement Electronics

The measurement circuit of the system is fundamentally an AC resistance measuring device. Appropriate verification and/or calibration of the measuring circuit is required for measurement systems with signal transfer via analog cable. This is accomplished by disconnecting the measuring circuit from the sensor's electrodes, attaching traceable resistors of known value with the cable of the measurement system to the measuring circuit, and verifying that the measured resistance agrees with the resistor value to an acceptable level. A typical acceptance criterion for the resistance accuracy is < 2 per cent of the reading at resistances $> 100 \Omega$, and increasing to 5 per cent at lower resistances. However, the application criticality should ultimately determine the desired accuracy.

For conductivity systems that cannot have the resistance-measuring circuit disconnected from the electrodes (e.g., measurement circuit and electrodes in one mutual housing), it may be difficult to directly adjust or verify the circuit accuracy, depending on the sensor design. An alternative method of verifying the measurement system integrity is a system calibration according to the procedures for the cell constant determination for each measuring circuit that is intended to be used.

If verification/calibration of the sensor's cell constant, temperature device, and measuring circuit are done at the same service interval, the measuring circuit should be verified first, the temperature device next, and the cell constant last. Because all of these parameters are typically very stable due to modern electronics and stable sensor construction, frequent calibration (such as daily) is not usually required. Comparison to qualified reference systems is also a proper means of calibration. Calibration is performed at appropriate intervals as defined in the quality management system.

Temperature Compensation

Because the conductivity of a fluid is temperature dependent, temperature compensation of the conductivity measurement is necessary unless otherwise prescribed (e.g., purified water, water for injection). An appropriate temperature compensation algorithm will ensure that changes in the conductivity measurement can be ascribed to concentration changes and not temperature changes. Conductivity measurements are normally referenced to 25° . A common form of linear temperature compensation uses Equation 4:

$$\kappa_{25} = \frac{\kappa_T}{[1 + \alpha(T - 25)]}$$

κ_{25} = conductivity compensated to 25°

κ_T = conductivity at T

α = temperature coefficient of the conductivity

T = measured temperature

A temperature coefficient of 2.1 per cent per 1° is commonly used for many salt solutions. Most salt-based solutions have linear compensation factors ranging from 1.9 per cent to 2.2 per cent per 1° . Depending on the fluid samples, other forms of temperature compensation may be appropriate. Non-linear temperature compensation data for a variety of solutions is widely available (e.g., as described in *ISO 7888 Water quality—Determination of electrical conductivity*). In cases of very low conductivity ($< 10 \mu\text{S}/\text{cm}$), such as purified water for cleaning/rinsing purposes, two compensations need to be made. One is for the intrinsic conductivity of water, and the other is for the other ionic

species in water. These compensations are normally combined and embedded in the microprocessor-controlled conductivity measurement systems. This is not supplied in all conductivity measurement technologies.

Conductivity Measurement of Fluids

For off-line or at-line batch measurements, rinse the cleaned sensor with the fluid to be measured. Then immerse the sensor in the fluid to be measured, and record the temperature and the temperature-compensated conductivity as required. Be sure that the position of the sensor in the container does not affect the conductivity measurement, because the container walls can affect the measurement for some electrode designs.

For continuous on-line or in-line measurements, install the cleaned sensor into the pipe, tank, or other containment vessel, and flush, if necessary. Make sure proper installation procedures are applied to prevent bubbles or particles from collecting between the electrodes. Be sure that the position of the sensor in the pipe or tank does not affect the conductivity measurement, because the nearby surfaces can affect the measurement for some electrode designs.

Record the temperature and the temperature-compensated conductivity as required.

For all batch or continuous measurements, ensure that the wetted components of the sensor are compatible with the fluid and the temperature to be measured.

◆ **Water conductivity.** A three-stage method of testing is described for Purified Water and Water for Injections (WFI). Testing at the first stage is usually adequate for Purified Water. Testing at two preliminary stages is given for WFI. If the test conditions and conductivity limits are met at either of these preliminary stages, the water meets the requirements of the test. In such cases proceeding to the third stage may not be necessary. Only in the event of failure at the final stage is the sample to be considered as not complying with the requirements of the test.

Stage 1 of the procedure may alternatively be performed on-line (with suitable modifications of the first step) with instrumentation that has been appropriately calibrated, whose cell constants have been accurately determined, and whose temperature compensation has been disabled. Prior to testing it must be ensured that such instrumentation has been suitably located and fitted in the water system.

Procedure

Stage 1.

1. Measure the temperature of the *water* using a non-temperature compensated conductivity reading. The measurement may be done in a suitable container or as an on-line determination.
2. Using Table 1/ Table 2 find the temperature value that is not greater than the measured temperature and read the corresponding conductivity value that becomes the limit (*Do not interpolate*).
3. If the measured conductivity is not greater than the table value, the *water* meets the requirements of the test. If the conductivity is higher than the table value, proceed with testing at stage 2.

Table 1

Temperature (°)	Purified Water Conductivity ($\mu\text{S cm}^{-1}$)
0	2.4
10	3.6
20	4.3
25	5.1
30	5.4
40	6.5
50	7.1
60	8.1
70	9.1

75	9.1
80	9.7
90	9.7
100	10.2

Table 2

Temperature (°)	Water for Injections and Sterile Water for Injections/ Inhalation Conductivity ($\mu\text{S cm}^{-1}$)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Stage 2.

- Transfer a sufficient amount of water (100 ml or more) to a suitable container, and stir the test sample. Adjust the temperature, if necessary, and while maintaining it at $25 \pm 1^\circ$, begin vigorously agitating the sample while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than $0.1 \mu\text{S cm}^{-1}$ per 5 minutes, note the conductivity.
- If the conductivity is not greater than $2.1 \mu\text{S cm}^{-1}$, the *water* under examination meets the requirements of the test. If the conductivity is greater than $2.1 \mu\text{S cm}^{-1}$, proceed with the testing at stage 3. For Sterile Water for Inhalation/Sterile Water for Injections: For containers with a nominal volume of 10 ml or less, if the conductivity is ~~NMT~~ not more than $25 \mu\text{S cm}^{-1}$, the water meets the requirements. For containers with a nominal volume greater than 10 ml, if the conductivity is ~~NMT~~ not more than $5 \mu\text{S cm}^{-1}$, the water meets the requirements.

Stage 3.

- Perform this test within approximately 5 minutes of the conductivity determination in step 5 under stage 2, while maintaining the sample temperature at $25 \pm 1^\circ$. Add a recently prepared saturated solution of *potassium chloride* to the test sample (0.3 ml per 100 ml of the test sample), and determine the pH (2.4.24) to the nearest 0.1 pH unit.
- Using Table 3, determine the conductivity limit at the measured pH value in step 6. If the measured conductivity in step 4 under stage 2 is not greater than the conductivity requirements for the pH determined, the water under

examination meets the requirements of the test. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0 to 7.0, the water under examination does not meet the requirements of the test.

Table 3

pH	Conductivity ($\mu\text{S cm}^{-1}$)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.2
6.5	2.2
6.6	2.2
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6



DRAFT FOR COMMENTS