

Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

2.4.24 pH Values

Published on: 20.01.2025

Last date for comments: 07.03.2025

This draft proposal contains general chapter 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. 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

Description	Details
Document version	1.0
Monograph proposed for inclusion	IP 2026
Tentative effective date of monograph	July, 2026
First draft published on IPC website for public comments	20.01.2025
Draft revision published on IPC website for public comments	-
Further follow-up action as required.	

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Change to: 2.4.24. pH Values

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. In the Pharmacopoeia, standards and limits of pH have been provided for those Pharmacopoeial substances in which pH as a measure of the hydrogen-ion activity is important from the standpoint of stability or physiological suitability. The determination is carried out at a temperature of $25^{\circ} \pm 2^{\circ}$, unless otherwise specified in the individual monograph. The pH of an aqueous solution is defined as the negative logarithm of the activity of its hydrogen ions, expressed conventionally as the hydrogen ion concentration of the solution. For practical purposes, its definition is an experimental one. The pH of a solution to be examined is related to that of a reference solution (pH_s) by the following equation:

$$\text{pH} = \text{pH}_s - [(E - E_s) / k]$$

in which E is the potential, expressed in volts, of the cell containing the solution to be examined and E_s is the potential, expressed in volts, of the cell containing the solution of known pH (pH_s), k is the change in potential per unit change in pH, expressed in volts (Table -1) and calculated from the Nernst equation.

Table-1: Values of k for Various Temperatures

Temperature of Solution (°)	k (V)
15	0.0572
20	0.0582
25	0.0592
30	0.0601
35	0.0611

The potentiometric determination of pH is made by measuring the potential difference between 2 appropriate electrodes immersed in the solution to be examined; one of these electrodes is sensitive to hydrogen ions (usually a glass electrode) and the other is the reference electrode (e.g. a silver-silver chloride electrode). They are often combined as 1 compact electrode, together with a temperature probe.

Apparatus

The measuring apparatus is usually a voltmeter with an input resistance at least 100 times that of the electrodes used. It is normally graduated in pH units and has a sensitivity such that discrimination of at least 0.05 pH unit or at least 0.003 V may be achieved.

Recent pH meters are microprocessor-controlled and are operated using the manufacturer's firmware or software, according to given instructions.

Operate the pH meter according to the manufacturer's instructions. Calibrate the apparatus using buffer solution of *potassium hydrogen phthalate 0.05M* as the primary standard, adjusting the meter to read the appropriate pH value given in the Table-2, corresponding to the temperature of the solution. To set the scale, use a second reference buffer solution, either buffer solution of *potassium tetroxalate 0.05M*, buffer solution of *potassium dihydrogen phosphate 0.025M + disodium hydrogen phosphate 0.025M* or buffer solution of *disodium tetraborate 0.01M* and carry out a check with a third buffer solution of intermediate pH. The pH reading of the intermediate solution must not differ by more than 0.05 from the corresponding value indicated in the Table.

Management of Electrodes. The electrodes are stored appropriately and according to the manufacturer's recommendations (e.g. in an electrolyte solution or a suitable storage solution). Before measurement, the electrodes are visually checked. Refillable electrodes are checked for the absence of air bubbles in the glass bulb and to ensure that the inner electrolyte solution level is satisfactory. The filling orifice has to remain open during the measurement. It is also recommended that the diaphragm of the reference electrode is checked. Before first use, or if the electrode has been stored out of electrolyte solution, it is usually necessary to condition it, according to the recommendations of the manufacturer. If pH stabilisation is too slow (i.e. a long response time), or a zero-point shift, reduced slope or any other difficulties in calibration are observed, the electrode will probably need to be cleaned or replaced. The cleaning is performed depending on the type of sample and as prescribed in the manufacturer's manual. Regular cleaning is recommended.

Calibration. Because of variations in the nature and operation of the available pH measurement systems, it is not practical to provide universal directions for the calibration of the measurement system. However, the general principles to be followed are set forth in the following paragraphs. Examine the electrodes, especially the reference electrode and electrolyte level, if a liquid electrolyte is used. If necessary, replenish electrolyte supply, and observe other precautions indicated by the instrument and electrode manufacturers.

The calibration or verification of the pH measurement system should be periodically executed. The historical performance of the measurement system, the maintenance of the pH sensor, and the frequency of measurement operation are used to determine the frequency of the calibration/verification. The procedure below allows for several calibration methodologies (two-point calibration, multiple-point calibration, and multiple-segment calibration).

If the pH of the buffer is sensitive to ambient carbon dioxide, then use Purified Water that has been recently boiled, and subsequently stored in a container designed to minimize ingress of carbon dioxide.

1. To calibrate the pH measurement system, select three buffer solutions for calibration, preferably from those given in Table-2, such that the expected pH of the material under test falls within their range. Two of the buffers are used for the calibration process, and the third buffer is used for verification. The value of the verification buffer shall be between two of the calibration buffers. If the operation range of the pH sensor is beyond the pH range of the buffer solutions in Table-2, then either 1) select two nearby pH buffers from Table-2 or 2) select one from Table-2 and another documented prepared buffer that is outside the range.
2. Rinse the pH sensor several times with water, then with the first buffer solution
3. Immerse the pH sensor in the first buffer solution at a temperature within the range of Table-2
4. If automatic temperature measurement and compensation are not included in the measuring system, manually enter the temperature of the buffer and pH value of the buffer solution at that temperature into the instrument. For temperatures not listed in Table-2, use linear interpolation to determine the pH value as a function of temperature.
5. Initiate the two-point calibration sequence with the first buffer according to the manufacturer's instruction.
6. Remove the pH sensor from the first buffer and rinse the electrode(s) with water, and then with the second buffer solution.
7. Immerse the pH sensor in the second buffer at a temperature within the range of Table-2
8. If automatic temperature measurement and compensation are not included in the measuring system, manually enter the temperature of the buffer and pH value of the buffer solution at that temperature into the instrument.
9. Continue the two-point calibration sequence with the second buffer according to the manufacturer's instructions.
10. After completion of the two-point calibration process, verify that the pH slope and offset are within acceptable parameters. Typical acceptable parameters are a slope of 90 per cent to 105 per cent and an offset of 0 ± 30 mV (0.5 pH units at 25°). Depending on the pH instrumentation, the pH slope and offset may be determined in software or by manual methods. If using manual methods, follow supplier instructions to calculate the pH sensor slope/offset. If these parameters are not within acceptable parameters, the sensor should be properly cleaned, replenished, serviced, or replaced, and the two-point calibration process shall be repeated.
11. Remove the pH sensor from the second buffer, and rinse thoroughly with water, and then the verification buffer.
12. Immerse the pH sensor in the verification buffer at a temperature within the range of Table-2.
13. If automatic temperature measurement and compensation are not included in the measuring system, manually enter the temperature of the buffer and pH value of the buffer solution at that temperature into the instrument.
14. The pH reading shall be within ± 0.05 of the value in Table-2 at the buffer solution temperature.

Note: If a multiple-point calibration process (three or more calibration buffers) plus at least one verification buffer are used, then repeat steps 9–14, assuring that the pH sensor slope and offset criteria (see step 10) and the calibration accuracy (see step 14) of this range are met. The value of the verification buffers shall be between the highest and lowest calibration buffers of the range.

Note: If a multiple-segment calibration process (three or more calibration buffers with at least two slopes and offsets) plus at least verification buffer for each segment are used, then repeat steps 9–14 for each segment, assuring that the pH sensor slope and offset criteria (see step 10) and the calibration accuracy (see step 14) of each segment are met. The value of each verification buffer shall be between the highest and lowest calibration buffers for each segment.

Table-2: pH of reference buffer solutions at various temperatures

Temp (°)	Potassium tetra oxalate 0.05M	Potassium hydrogen tartrate saturated at 25°	Potassium dihydrogen citrate 0.05 M	Potassium hydrogen phthalate 0.05 M	Potassium dihydrogen phosphate 0.025 M + Disodium hydrogen phosphate 0.025 M	Potassium dihydrogen phosphate 0.0087 M + Disodium hydrogen phosphate 0.0303 M	Disodium tetraborate 0.01 M	Sodium carbonate 0.025 M + Sodium bicarbonate 0.025 M	Calcium hydroxide, saturated at 25°
	C ₄ H ₃ KO ₈ ,2H ₂ O	C ₄ H ₅ KO ₆	C ₆ H ₇ KO ₇	C ₈ H ₅ KO ₄	KH ₂ PO ₄ + Na ₂ HPO ₄	KH ₂ PO ₄ + Na ₂ HPO ₄	Na ₂ B ₄ O ₇ , 10H ₂ O	Na ₂ CO ₃ + NaHCO ₃	Ca(OH) ₂
15	1.67		3.80	4.00	6.90	7.45	9.28	10.12	12.81
20	1.68		3.79	4.00	6.88	7.43	9.23	10.06	12.63
25	1.68	3.56	3.78	4.01	6.87	7.41	9.18	10.01	12.45
30	1.68	3.55	3.77	4.02	6.85	7.40	9.14	9.97	12.29
35	1.69	3.55	3.76	4.02	6.84	7.39	9.10	9.93	12.13
Δ pH (1)/ Δ°	+0.001	-0.0014	-0.0022	+0.0012	-0.0028	-0.0028	-0.0082	-0.0096	-0.034

(1) pH variation per degree Celsius.

Preparation of Reference Buffer Solutions

Potassium tetra oxalate 0.05 M. Dissolve 12.61 g of C₄H₃KO₈,2H₂O in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Potassium hydrogen tartrate, saturated at 25 °. Shake an excess of C₄H₅KO₆ vigorously with *carbon dioxide-free water* at 25°. Filter or decant. Prepare immediately before use.

Potassium dihydrogen citrate 0.05 M. Dissolve 11.41 g of C₆H₇KO₇ in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent. Prepare immediately before use.

Potassium hydrogen phthalate 0.05 M. Dissolve 10.13 g of C₈H₅KO₄, previously dried for 1 hour at 110 ± 2°, in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Potassium dihydrogen phosphate 0.025 M + Disodium hydrogen phosphate 0.025 M. Dissolve 3.39 g of KH₂PO₄ and 3.53 g of Na₂HPO₄, both previously dried for 2 hours at 120 ± 2°, in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Potassium dihydrogen phosphate 0.0087 M + Disodium hydrogen phosphate 0.0303 M. Dissolve 1.18 g of KH₂PO₄ and 4.30 g of Na₂HPO₄, both previously dried for 2 hours at 120 ± 2°, in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Disodium tetraborate 0.01 M. Dissolve 3.80 g of Na₂B₄O₇,10H₂O in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Sodium carbonate 0.025 M + Sodium hydrogen carbonate 0.025 M. Dissolve 2.64 g of Na₂CO₃ and 2.09 g of NaHCO₃ in *carbon dioxide-free water* and dilute to 1000.0 ml with the same solvent.

Calcium hydroxide, saturated at 25°. Shake an excess of calcium hydroxide Ca(OH)₂ with *carbon dioxide-free water* and decant at 25°.

If suspensions, emulsions or solutions of non-aqueous or partially non-aqueous character are measured on a system calibrated as described above, the pH reading can only be considered to be an approximation of the true value. Suitable electrodes have to be used for pH measurements of such mixtures.

Storage of Buffer Solutions

Store buffer solutions in suitable chemically-resistant, airtight containers, such as type I glass bottles or plastic containers suitable for aqueous solutions.

Approximate pH of Solutions

Determine the approximate pH using a pH indicator strip. Alternatively, pH indicators such as those described in Table-3 can be used.

Table-3

Reaction	pH	Indicator
Alkaline	>8	<i>Red litmus paper</i>
Slightly Alkaline	8-10	<i>Phenolphthalein solution</i> <i>Thymol blue solution</i>
Strongly Alkaline	>10	<i>Phenolphthalein paper</i> <i>Thymol blue solution</i>
Neutral	6-8	<i>Methyl red solution</i> <i>Phenol red solution</i>
Acid	< 6	<i>Methyl red solution</i> <i>Bromothymol Blue Solution</i>
Slightly acid	4-6	<i>Methyl red solution</i> <i>Bromocresol green solution</i>
Strongly acid	< 4	<i>Congo red paper</i>