Reagents for Pharma Industry

Chapter 1

PanReac AppliChem
ITW Reagents

Summary

PanReac AppliChem
ITW Reagents

Other Chapters of Reagents for Pharma Industry

Chapter 2
Physical and physicochemical methods (Ph. Eur. 2.2.) - Spectroscopy

Chapter 3
Biological tests (Ph. Eur. 2.6.)
Biological assays (Ph. Eur. 2.7.)

Chapter 4
Physical and physicochemical methods (Ph. Eur. 2.2.) - Chromatography

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Chapter 7
Waste water analysis

Chapter 8
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About Us

The Origin

ITW Illinois Tool Works Inc. (NYSE: ITW) is a global industry company that delivers specialized expertise, innovative thinking and value-added products to meet critical customer needs in a variety of industries.

ITW, with approximately 14 billion dollars in global revenues, operates 7 major segments with businesses in 58 countries that employ approximately 50,000 employees. The company has a broad portfolio of more than 17,000 global patents and patent applications.

The ITW Reagents Division

In 2010, the ITW Reagents division was born integrated by the companies Panreac Química SLU (Spain) and Nova Chimica Srl (Italy), and later on by AppliChem GmbH (Germany). The division offers the highest quality and innovative products for analysis, research and production applications.

ITW Reagents markets its products worldwide through an extensive distribution network to more than 80 countries under the PanReac AppliChem brand. It has two production plants in Darmstadt (Germany) and Barcelona (Spain).

1912 ITW → 1941 Panreac Química → 1980 Nova Chimica → 1992 AppliChem

We are Everywhere

We can say that almost all products subject to human manipulation have undergone chemical analysis that guarantees their physical and chemical properties. Food, agrifood, medicines, cosmetics... and so many other products are subjected to chemical analysis. Our reagents can be found in any quality control and research laboratory.

Our range of Laboratory Chemicals include:

Analytical reagents
Reagents for volumetric analysis
Reagents and solvents for general applications
Reagents and solvents for HPLC
Reagents and solvents for GC
Reagents for metallic traces analysis
Analytical standards
Reagents and solvents for specific applications
Products for clinical diagnosis
Products for microbiology

Our range of Laboratory Biochemicals cover:

Cell Biology / Cell Culture
Protein Biochemistry and Electrophoresis
Nucleic Acid Biochemistry
General Biochemicals and Biological Buffers
Special Biochemicals

Service & Benefits

Exceptional know-how and a wide range of chemicals and biochemicals for a great diversity of applications.

European production committed to corporate social responsibility (CSR).

Efficient global distribution network to export our products worldwide to more than 80 countries.

Qualified management team fully committed to our business project.

Excellence

Our products are strictly controlled in our laboratories and meet the highest quality requirements. A multi-site Integrated Management System for Quality, Environment and Safety is implemented in all activities and processes.

ISO 9001:2015 | ISO 14001:2015 | OHSAS 18001:2007

Introduction

The **Pharmaceutical Industry** discovers, develops, produces, and markets drugs or **pharmaceutical drugs** for use as medications.

Pharmaceutical companies may deal in **generic** or **brand medications** and medical devices.

They are subject to a variety of **laws** and **regulations** that govern the patenting, testing, safety, efficacy and marketing of drugs.

The pharmaceutical industry is largely driven by **scientific discovery** and **development**, in conjunction with **toxicological** and **clinical experience**.

Major differences exist between **large organizations** which engage in a broad range of drug discovery and development, manufacturing and quality control, marketing and sales and **smaller organizations** which focus on a specific aspect.

Most multinational pharmaceutical companies are involved in all these activities; however, they may specialize in one aspect based upon local market factors. Academic, public and private organizations perform scientific **research to discover and develop new drugs**. The biotechnology industry is becoming a major contributor to innovative pharmaceutical research. Often, collaborative agreements between research organizations and large pharmaceutical companies are formed to explore the potential of new drug substances.

Active drug substances (APIs, Active Principle Ingredient) and **inert materials** (Excipients) are combined **during pharmaceutical manufacturing** to produce dosage forms of medicinal products (e.g. tablets, capsules, liquids, powders, creams and ointments). Drugs may be categorized by their manufacturing process and therapeutic benefits.

The different pharmaceutical manufacturing processes each have their own **environmental issues** and the wastes must be treated and controlled. **For example:**

- During **fermentation process**, the spent fermentation broth contains sugars, starches, proteins, nitrogen, phosphates and other nutrients with high biochemical oxygen demand (BOD), chemical oxygen demand (COD) and total suspended solids (TSS) with pH values ranging from 4 to 8.
- Also, wastes from **chemical synthesis** are complex due to the variety of hazardous materials, reactions and unit operations. These waste waters are high in BOD, COD and TSS, with varying acidity or alkalinity and pH values ranging from 1 to 11.

The analysis laboratories play a fundamental role in the pharmaceutical industries. **They are key pieces in:**

- Discovery and improvement of a **drug.**
- Development and optimization of **manufacturing processes.**
- **Quality control** of raw materials, intermediates and finished products.
- Quality control of **wastes.**

!

Depending on the type of analysis in which they are involved, **different types of laboratories** can be distinguished within the same pharmaceutical company. Besides, the **type of analysis** and the techniques used may be different (as shown on the next page).

In any case, the methods of analysis must be strictly validated and follow the requirements set by the **Pharmacopoeias** (Ph. Eur., USP, etc.) both in the analysis protocols and in the quality of the reagents to be used.

Our **portfolio** includes a wide range of products such as solvents, acids, bases and salts indicated for general analytical applications that **fulfil the requirements indicated in the Pharmacopoeias** (Ph. Eur. or USP) for the reagents to be used for analytical purposes.

Reagents for Pharma Industry

Chapter 1

Types of Laboratories versus Methods of Analysis

Facility		R&D Centre		Manufacturing Plant Quality Control			Wastewater Plant
Laboratory		New molecules / Improvements of existing products	Analytical development	Raw Material (excipients & APIs)	In-process (intermediate product)	Final product	Water quality control
Methods of analysis	Chapter						
Amino acid analysis	5			●	●	●	
Ammonium	6/7						●
Approximate pH of solutions	1		●	●	●	●	●
Assay: Protein (Kjeldahl)	6		●	●			
Assay: Titration	6		●	●			
Assay: Water (KF)	6		●	●	●	●	
Atomic Absorption spectroscopy	2		●	●			
Biological assays	3		●	●			
Biological tests	3			●		●	
Clarity and opalescence of liquids	1		●	●		●	
Chlorinated compounds	7						●
Conductivity	1		●	●			
Degree of Coloration of Liquids	1		●	●			
Detergents (Surfactants)	7						●
Dissolution Test	1					●	
Electrophoresis	5	●	●	●	●	●	
Gas Chromatography	4	●	●	●		●	
ICP	2		●	●			
Identification	6		●	●		●	
IR	2	●	●	●		●	
Limit tests	6		●	●			
Liquid Chromatography	4	●	●	●		●	
Molecular mass distribution in dextrans	5			●	●		
Organic compounds (COD, DBO5, TOC)	7						●
Peptide identification by NMR spectrometry	5	●	●	●	●	●	
Peptide mapping	5	●		●	●	●	
Phosphates	6/7						●
Potentiometric determination of pH	1		●	●	●	●	●
Residual catalyzers (Metals, Cyanides)	7						●
Suspended matter	7						●
Thin Layer Chromatography	4	●	●	●			
UV	2	●	●	●			
Synthesis*	8	●					

*not a method of analysis but reagents and solvents involved in synthesis procedures.

In the following sections we will describe the most common methods of analysis indicated in the pharmacopoeias and offer the most appropriate reagents for each method.

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Degree of Coloration of Liquids

The examination of the degree of coloration of liquids in the range brown-yellow-red is carried out comparing visually the sample color with a scale of different standard solutions.

These solutions are prepared from 3 primary color standard solutions (yellow, red and blue) that are mixed and diluted with hydrochloric acid (10 g/L) at different concentrations to finally make 37 reference liquid color standards: 9 Brown (B1 - B9), 7 Brownish-Yellow (BY1 – BY7), 7 Yellow (Y1 – Y7), 7 Greenish-Yellow (GY1 – GY7) and 7 Red (R1 – R7).

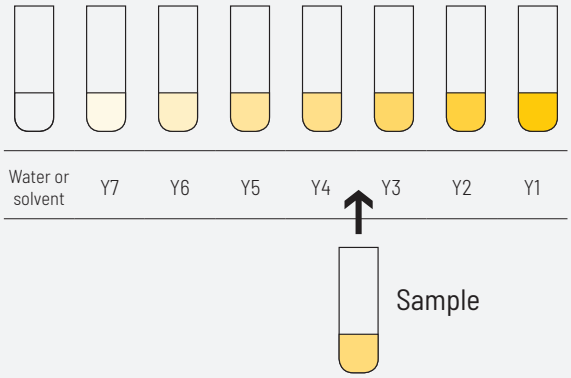
A solution is colorless if it has the appearance of water or the solvent or is not more intensely colored than reference solution B9.

There are 2 possible methods to determine de degree of coloration of liquids depending on the type of glass tube used and depending on the situation of a white background (horizontally or vertically).

Method 1

Tubes of colorless, transparent, neutral glass of 12 mm external diameter.

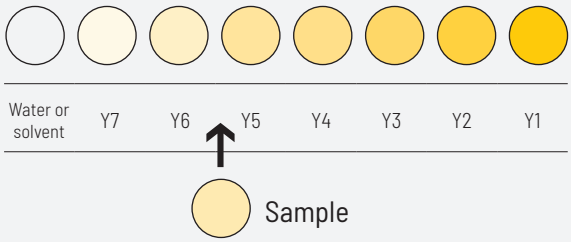
Compare the colors in diffused daylight, viewing horizontally against a white background.



Method 2

Tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm.

Compare the colors in diffused daylight, viewing vertically against a white background.



Primary color standard solutions according to pharmacopoeia requirements

Product name	Composition	Ph. Eur., BP	USP, FCC	Code	Package
Yellow Primary Solution (BP, Ph. Eur.) for analysis	45.00 ± 0.05 g $FeCl_3.6H_2O$ in 1 L of 1 % HCl	Yellow Primary Solution	Ferric Chloride - SC	125415.1208	100 mL
Blue Primary Solution (BP, Ph. Eur.) for analysis	62.40 ± 0.05 g $CuSO_4.5H_2O$ in 1 L of 1 % HCl	Blue Primary Solution	Cupric Sulfate - SC	125417.1208	100 mL
Red Primary Solution (BP, Ph. Eur.) for analysis	59.5 ± 0.1 g $CoCl_2.6H_2O$ in 1 L of 1 % HCl	Red Primary Solution	Cobalt Chloride - SC	125416.1208	100 mL
Auxiliary reagent: Hydrochloric Acid 10 %				123006.1211	1000 mL

Clarity and degree of opalescence of liquids

This determination can be performed Visually or with Instrumental Methods as Nephelometry or Turbidimetry.

Visual Method

The liquid to be examined is compared in diffused daylight with reference suspensions, freshly prepared, viewing vertically against a black background.

The **Primary Opalescent Suspension** (formazin suspension) is prepared by mixing equal volumes of a hydrazine sulfate solution and hexamethylenetetramine solution. This formazin suspension has to be allowed to stand 24 h and it is stable for 2 months when stored in a glass bottle. This solution is defined as a 4000 NTU (Nephelometric Turbidity Units).

The **Standard of Opalescence** (60 NTU) is obtained by diluting 15.0 mL of Primary Opalescent Suspension to 1000.0 mL.

The **Reference Suspensions** are prepared by diluting with water the Standard of Opalescence.

Reference suspensions I, II, III and IV have values of 3 NTU, 6 NTU, 18 NTU and 30 NTU respectively.

A liquid is considered clear if its clarity is the same as that of water or of the solvent used or its opalescence is not more pronounced than that of a reference suspension.

Reference suspensions
They are prepared by diluting the Standard of Opalescence (60 NTU).

Reference suspensions		I	II	III	IV
% Standard of Opalescence	Water or solvent	5% (v/v)	10% (v/v)	30% (v/v)	50% (v/v)
Nephelometric Turbidity Units		3 NTU	6 NTU	18 NTU	30 NTU

Sample

We offer the 2 standard solutions according to pharmacopoeia requirements in order to prepare the Primary Opalescent Suspension:

Product name	Composition	Code	Package
Turbidity Primary Standard Solution A	1.0 g Hydrazinium Sulfate in 100 mL water	395464.1209	250 mL
Turbidity Primary Standard Solution B	10.0 g Hexamethylenetetramine in 100 mL water	395465.1209	250 mL

To obtain the 4000 NTU suspension (primary opalescent suspension), mix 5 ml of Turbidity Standard solution A with 5 ml of Turbidity Standard solution B and allow to stand for 24 hours at 25°C. The required standard solutions can be prepared from this standard by dilution with water. Shake the standard suspension before use. This suspension is stable for 2 months when stored in a glass bottle.

Instrumental Methods

The degree of opalescence may also be determined by instrumental measurement of the light absorbed or scattered on account of submicroscopic optical density inhomogeneities of opalescent solutions and suspensions.

Nephelometry

When electromagnetic radiation (light) strikes a particle in solution, some of the light will be absorbed by the particle, some will be transmitted through the solution and some of the light will be scattered or reflected.

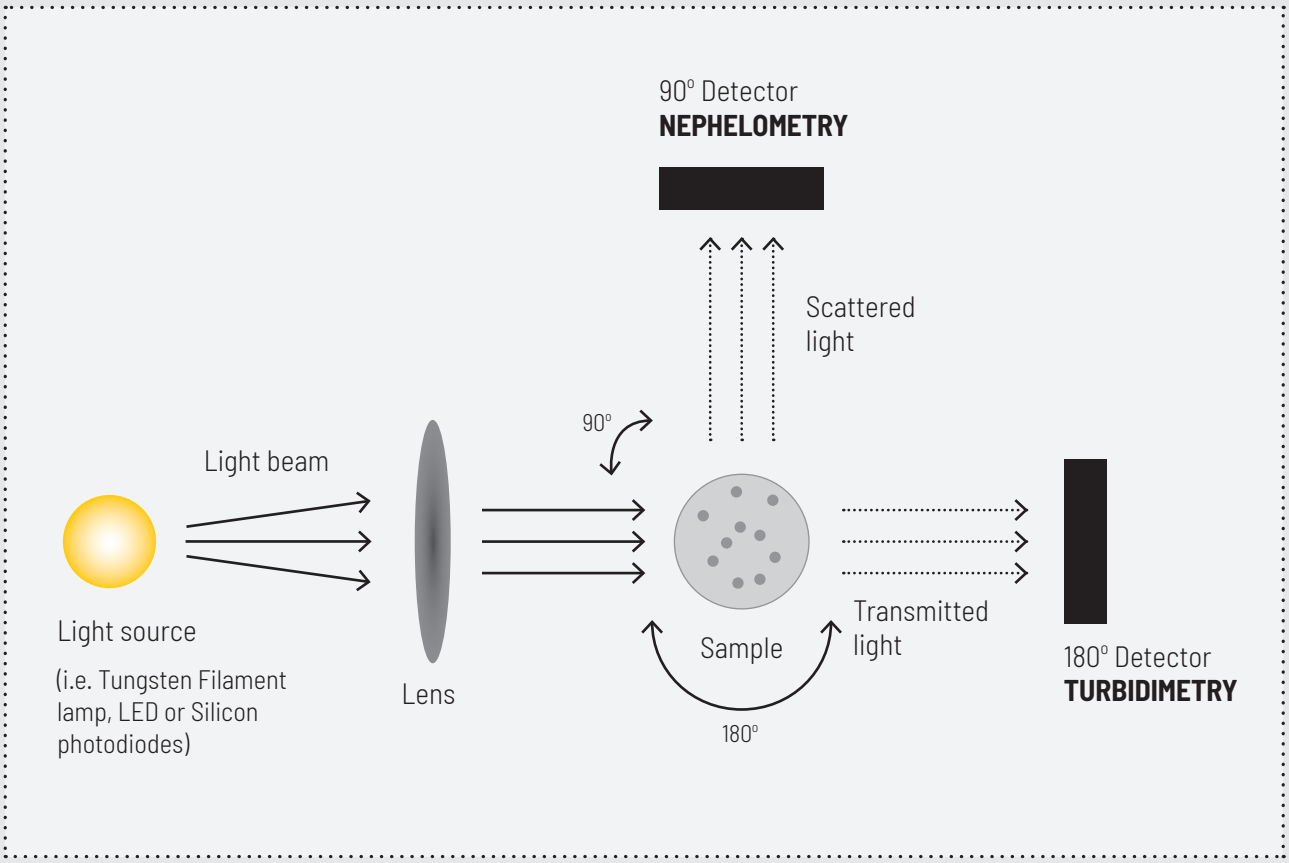
If measurement is made at 90^0 to the light beam, the light scattered by the suspended particles can be used for the determination of their concentration. The amount of light scattered is proportional to the concentration of insoluble particle.

The reference suspensions must maintain a constant degree of turbidity and the sample and reference suspensions must be prepared under identical conditions.

The maximum nephelometric values at which reliable measurements can be made lie in the range of 1750-2000 NTU. As the degree of turbidity increases, not all the particles are exposed to the incident light and the scattered radiation of other particles is hindered on its way to the detector.

Turbidimetry

The optical property expressed as turbidity is the interaction between light and suspended particles in liquid. This is an expression of the optical property that causes light to be scattered and absorbed rather than transmitted in a straight line through the sample.



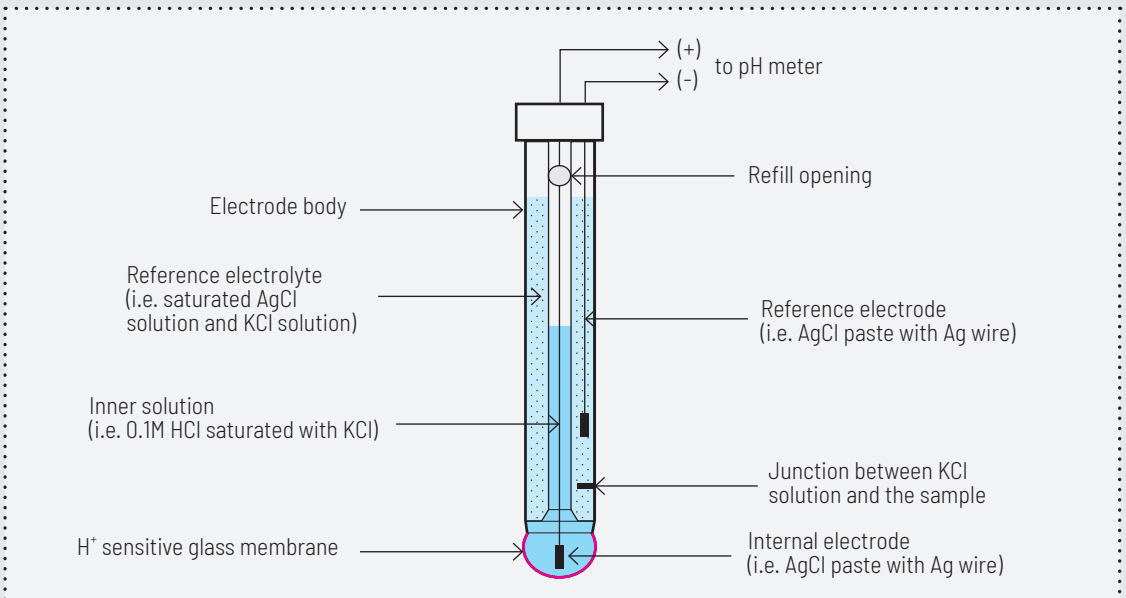
The instruments used are verified using the reference suspensions described under the Visual method.

Potentiometric determination of pH

The pH is a numeric scale used to specify the acidity or basicity of an aqueous solution.

The potentiometric determination of pH is made in a voltmeter by measuring the potential difference between two appropriate electrodes immersed in the solution to be examined.

One of the electrodes is sensitive to hydrogen ions (usually a glass electrode) and the other is the reference electrode (e.g. a silver chloride electrode). They are often combined as one compact electrode together with a temperature probe.



A Standard Glass Combination pH Electrode

The calibration of the equipment has to be performed on a regular basis, preferably each day of use or before each series of measurement.

We offer a wide range of NIST SRM-traceable pH buffer solutions for the calibration of pH meters. This range of buffers includes both concentrated buffer solutions and ready-to-use buffer solutions.

All these solutions are very stable and can be stored for long time periods (up to 6 years).

An accuracy of ± 0.02 pH units, at a temperature of 20 °C, is guaranteed in most cases.

The label on each container indicates its composition, batch number, expiry date and pH variation with temperature for better control of quality management.

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Ready-to-use colorless Buffer Solutions

pH value (20 °C)	Components (aqueous solution)	Code	Package
1.00 ± 0.02	Glycine Sodium Chloride Hydrochloric Acid	272580.1211	1000 mL
1.675 ± 0.01	Potassium Tetraoxalate	277126.1209	250 mL
2.00 ± 0.02	Citric Acid Sodium Hydroxide Hydrochloric Acid	272581.1209	250 mL
		272581.1211	1000 mL
3.00 ± 0.02	Citric Acid Sodium Hydroxide Hydrochloric Acid	272537.1209	250 mL
		272537.1211	1000 mL
3.20 ± 0.02	di-Sodium Hydrogen Phosphate Citric Acid	275653.1214	5 L
4.00 ± 0.02	Citric Acid Sodium Hydroxide Hydrochloric Acid	272168.1209	250 mL
		272168.1211	1000 mL
		272168.1214	5 L
		272168.1315	10 L
4.001 ± 0.01	Potassium Hydrogen Phthalate	277125.1211	1000 mL
5.00 ± 0.02	Citric Acid Sodium Hydroxide	272582.1211	1000 mL
6.00 ± 0.02	Citric Acid Sodium Hydroxide	272549.1211	1000 mL
6.88 ± 0.05	Potassium di-Hydrogen Phosphate di-Sodium Hydrogen Phosphate	277091.1211	1000 mL
6.881 ± 0.01	Potassium di-Hydrogen Phosphate di-Sodium Hydrogen Phosphate	277124.1211	1000 mL
7.00 ± 0.02	Potassium di-Hydrogen Phosphate di-Sodium Hydrogen Phosphate	272170.1209	250 mL
		272170.1210	500 mL
		272170.1211	1000 mL
		272170.1214	5 L
		272170.1315	10 L
7.02 ± 0.02	Potassium di-Hydrogen Phosphate di-Sodium Hydrogen Phosphate	273108.1211	1000 mL
8.00 ± 0.02	Boric Acid Sodium Hydroxide Hydrochloric Acid	272583.1211	1000 mL

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pH value (20 °C)	Components (aqueous solution)	Code	Package
9.00 ± 0.02	Boric Acid Potassium Chloride Sodium Hydroxide	272172.1211	1000 mL
9.225 ± 0.01	di-Sodium Tetraborate Sodium Azide	277123.1211	1000 mL
9.23 ± 0.02	Boric Acid Sodium Hydroxide	273107.1209	250 mL
		273107.1211	1000 mL
10.00 ± 0.05	Boric Acid Potassium Chloride Sodium Hydroxide	272584.1209	250 mL
		272584.1211	1000 mL
11.00 ± 0.05	Boric Acid Sodium Hydroxide	272585.1209	250 mL
		272585.1211	1000 mL
12.00 ± 0.05	di-Sodium Hydrogen Phosphate Sodium Hydroxide	272586.1209	250 mL
		272586.1211	1000 mL
12.627 ± 0.01	Calcium Hydroxide Sodium Azide	277089.1209	250 mL
13.00 ± 0.05	Potassium Chloride Sodium Hydroxide	272587.1211	1000 mL

Ready-to-use colored Buffer Solutions

Colored buffer solutions are easily identifiable in the laboratory

pH value (20 °C)	Components (aqueous solution)	Code	Package
4.00 ± 0.02 (red)	Citric Acid Sodium Hydroxide Hydrochloric Acid	273616.1209	250 mL
		273616.1211	1000 mL
		273616.1315	10 L
7.00 ± 0.02 (yellow)	Potassium di-Hydrogen Phosphate di-Sodium Hydrogen Phosphate	273617.1209	250 mL
		273617.1210	500 mL
		273617.1211	1000 mL
		273617.1214	5 L
		273617.1315	10 L
10.00 ± 0.05 (blue)	Boric Acid Potassium Chloride Sodium Hydroxide	273618.1211	1000 mL

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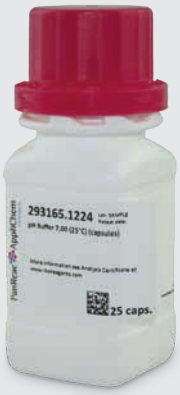
Buffer solutions - pH values depending on temperature

T (°C)	pH values																			
0	0.96	-	2.01	3.05	4.05	-	5.06	6.04	-	7.13	7.15	8.15	9.24	-	9.47	10.26	11.45	12.58	-	13.80
5	0.99	-	2.01	3.05	4.04	-	5.05	6.02	-	7.07	7.09	8.10	9.16	-	9.40	10.17	11.32	12.41	-	13.59
10	0.99	1.672	2.01	3.03	4.02	3.999	5.02	6.01	6.900	7.05	7.07	8.07	9.11	9.276	9.34	10.11	11.20	12.26	12.810	13.37
15	0.99	-	2.00	3.01	4.01	-	5.01	6.00	-	7.02	7.04	8.04	9.05	-	9.28	10.05	11.10	12.10	-	13.18
20	**1.00**	**1.675**	**2.00**	**3.00**	**4.00**	**4.001**	**5.00**	**6.00**	**6.881**	**7.00**	**7.02**	**8.00**	**9.00**	**9.225**	**9.23**	**10.00**	**11.00**	**12.00**	**12.627**	**13.00**
25	1.01	1.679	2.00	3.00	4.01	4.006	5.00	6.02	6.865	6.98	7.00	7.96	8.95	9.180	9.18	9.94	10.90	11.88	12.454	12.83
30	1.01	1.683	2.00	3.00	4.01	4.012	5.00	6.03	6.853	6.98	7.00	7.94	8.91	9.136	9.14	9.89	10.81	11.72	12.289	12.67
35	1.01	-	2.00	3.00	4.01	-	5.00	6.03	-	6.96	6.98	7.92	8.88	-	9.11	9.84	10.72	11.67	-	12.59
40	1.01	-	2.00	2.98	4.01	-	5.00	6.04	-	6.95	6.97	7.90	8.85	-	9.07	9.82	10.64	11.54	-	12.41
50	1.01	-	2.00	2.97	4.00	4.001	5.01	6.06	-	6.95	6.97	7.85	8.79	-	9.02	9.74	10.48	11.33	-	12.15

Concentrated Buffer Solutions

Concentrated buffer solutions save storage space. They are supplied in PE packs containing 25 capsules. Preparing the solution is as simple as dissolving the contents of a capsule in 100 mL of distilled water.

pH value (25 °C)	Code	Package
4.01 ± 0.02	293164.1224	25 capsules
7.00 ± 0.02	293165.1224	25 capsules
9.00 ± 0.02	293166.1224	25 capsules



pH values depending on temperature

T (°C)	pH values		
10	4.00	7.07	9.21
15	4.01	7.04	9.14
20	4.01	7.02	9.06
25	**4.01**	**7.00**	**9.00**
30	4.01	6.99	8.96
35	4.02	6.98	8.92
40	4.03	6.97	8.88
50	4.06	6.96	8.83
60	4.08	6.96	8.81

Electrolyte solutions

A regular pH electrode maintenance requires to check the level of the reference electrolyte and refill when necessary. Depending on the type of samples to analyze, different electrodes may be used and the recommended electrolyte also differs.

We supply three liquid electrolytes, that are the most commonly used solutions for the vast majority of electrodes.

Product name	Composition	Code	Package
Potassium Chloride saturated solution	35 g KCl in 100 mL H_2O	281495.1209	250 mL
Potassium Chloride 3 mol/l 	22.37 g KCl in 100 mL H_2O	282775.1209	250 mL
		282775.1211	1000 mL
		282775.1214	5 L
Potassium Chloride 3 mol/l + Silver Chloride	22.37 g KCl + 0.1 g AgCl in 100 mL H_2O	282923.1209	250 mL
		282923.1211	1000 mL

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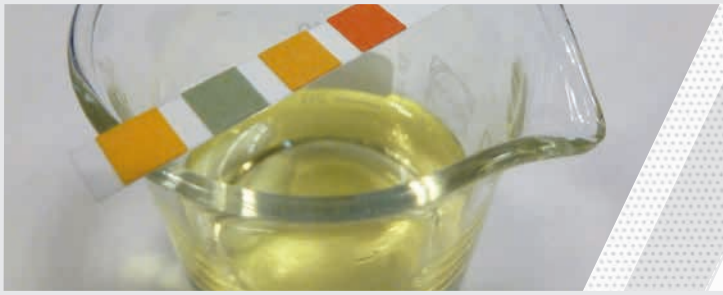
Approximate pH of solutions



The approximate pH of solutions can be determined using a pH indicator strip.

We offer a wide selection of ranges of reels and strips:

- The **pH indicator paper reels** are appreciated for many standard applications. For each pH value these papers show a single color which can be matched with the color scale at intervals of 0.5, 1 or 2 pH unit.
- For most precise reading, we offer a **triple zone pH-paper** that shows three different colors for each full pH unit. This tricolor paper is specially equipped with a hydrophobic barrier between the different indicators. As the different colors will not mix this ensures optimal usability.
- The **pH paper test strips** permit a quick determination since they do not need to be compared with a color scale. They are ideal for colored samples because any sample color has the same effect on both the reference color and the reactive pad.
- The **pH non-bleeding plastic strips** are specially suited for pH of dangerous, poisonous or aggressive liquids. The long plastic handle effectively protects the user from contact with the sample. The indicator is fixed to the test paper so the dye does not wash out and the sample remains pure for further analysis.

Product name	Presentation	Dimensions	Code
Universal Paper Reel pH 1-11 (gradation 1.0)	1 roll	7 mm x 5 m	524150.1825
Universal Paper Reel pH 1-14 (gradation 1.0/2.0)	1 roll	7 mm x 5 m	524151.1825
Special Paper Reel pH 5.5-9.0 (gradation 0.5)	1 roll	7 mm x 5 m	524152.1825
Tricolor Paper Reel pH 1-11 (gradation 1.0)	1 roll	10 mm x 5 m	524169.1825
Strips pH 3.8-5.5 (gradation 0.2/0.3)	200 strips	11 mm x 100 mm	524156.1826
Strips pH 6.0-8.1 (gradation 0.3)	200 strips	11 mm x 100 mm	524157.1826
Strips pH 1-12 (gradation 1.0)	200 strips	11 mm x 100 mm	524159.1826
Strips pH 5.2-6.8 (gradation 0.2/0.3)	200 strips	11 mm x 100 mm	524160.1826
Non bleeding sticks pH 0-14 (gradation 1.0)	100 sticks	6 mm x 85 mm	524164.1826
Non bleeding sticks pH 0.0-6.0 (gradation 0.5)	100 sticks	6 mm x 85 mm	524167.1826
Non bleeding sticks pH 4.5-10.0 (gradation 0.5)	100 sticks	6 mm x 85 mm	524165.1826
Non bleeding sticks pH 7.0-14.0 (gradation 0.5)	100 sticks	6 mm x 85 mm	524168.1826

Conductivity

The current (I) (in amperes) is the movement of charged particles (electrons in a metal wire and ions in a solution). The current flowing in a conductor is directly proportional to the applied electromotive force E (in volts) and inversely proportional to the resistance R **(in ohms, Ω)** of the conductor.

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

I: Current (A)
E: Electromotive force (V)
R: Resistance (Ω)

Resistivity (ρ) is a fundamental property that quantifies how strongly a given material or solution opposes the flow of electric current. A low resistivity indicates a material that readily allows the flow of electric current. It is defined as the quotient of the electric field and the density of the current. The unit of resistivity in the International System is expressed in ohm per metre (Ω·m). The resistivity of a solution is generally expressed in ohm per centimetres (**Ω·cm**).

$$R = \rho \frac{L}{S}$$

$$R = \frac{1}{k} \times \frac{L}{S}$$

ρ: Resistivity (Ω·cm)
L: Length of the conductor (cm)
S: Cross-section of the conductor (cm^2)
k: Conductivity ($S \cdot cm^{-1}$)

The conductivity (k) (formerly called specific conductance) of a solution is the inverse of resistivity. It is a measure of how easily the charge particles move through a solution/material across a specified distance. The unit of conductivity in the International System is the siemens per metre ($S \cdot m^{-1}$). In practice, the electrical conductivity of a solution is expressed in siemens per centimetre (**$S \cdot cm^{-1}$**).

$$k = \frac{1}{R} \times \frac{L}{S}$$

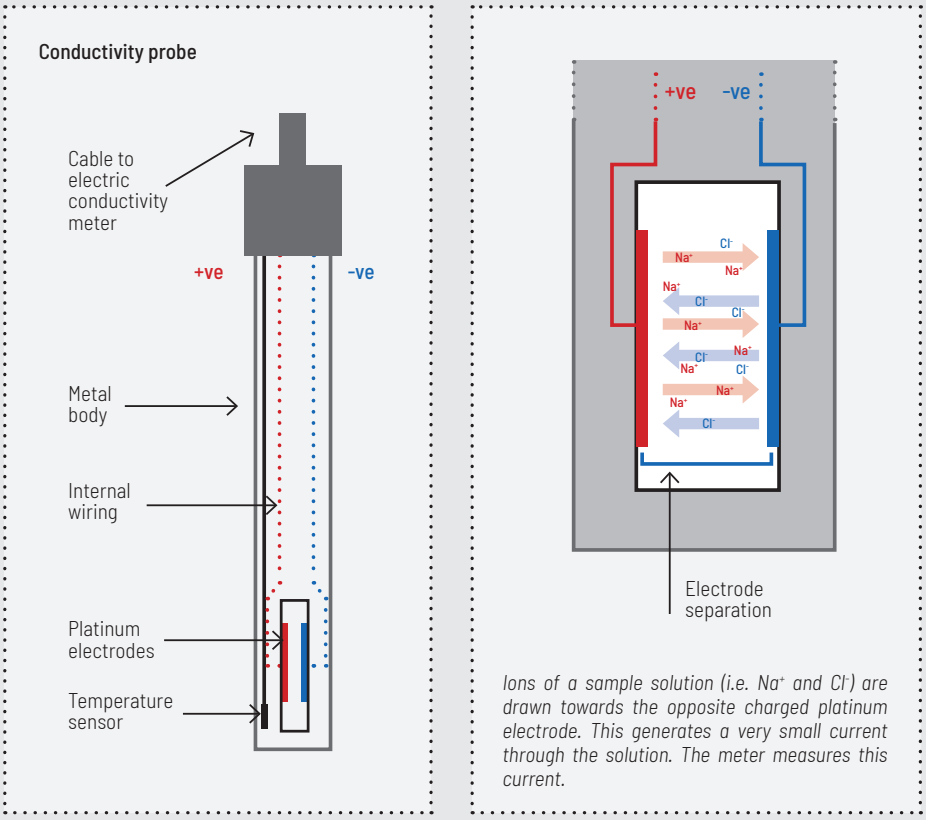
The **size** of the **current** in a solution depends on:

- Nature of the **ions**: charge, size and mobility
- Nature of the **solvent**: dielectric constant and viscosity
- **Concentration** of **ions**: the more ions the greater the conductivity and so conductivity can be used as a measure of concentration
- **Temperature**

Apparatus

The apparatus used (conductivity meter or resistivity meter) measures the resistance of the column of liquid between the electrodes of the immersed measuring device (conductivity cell). The apparatus is supplied with alternating current to avoid the effects of electrode polarization. It is equipped with a temperature probe and a temperature compensation device.

The conductivity cell contains 2 parallel platinum electrodes coated with platinum black, each with a surface area S, and separated from the other by a distance L. Both are generally protected by a glass tube.



Ions of a sample solution (i.e. Na^+ and Cl^-) are drawn towards the opposite charged platinum electrode. This generates a very small current through the solution. The meter measures this current.

Operating procedure

Choose a conductivity cell that is appropriate for the properties and conductivity of the solution to be examined.

Use a certified reference material for example a solution of potassium chloride, that is appropriate for the measurement, for calibrating the instrument at 25 °C ± 1 °C. The conductivity value of the certified reference material should be near the expected conductivity value of the solution to be examinated.

After calibrating the apparatus, rinse the conductivity cell several times with distilled water and at least twice with the aqueous solution to be examined. Carry out successive measurements as described in the monograph.

Conductivity standards

We supply different conductivity standards NIST traceable. They are accompanied by their corresponding certificate of analysis.

The product label indicates the composition, the variation of conductivity with the temperature and the expiry date for better quality assurance.

Conductivity nominal value at 25 °C	Composition (KCl)	Code	Package
84 µS/cm	0.00056 mol/L	396882.1209	250 mL
147 µS/cm	0.001 mol/L	396881.1209	250 mL
1413 µS/cm	0.010 mol/L	394659.1209	250 mL
5446 µS/cm	0.040 mol/L	394657.1209	250 mL
12.88 mS/cm	0.100 mol/L	394658.1209	250 mL

Conductivity values depending on temperature

T (°C)	Conductivity (mS/cm)				
20.0	0.0758	0.133	1.278	4.915	11.67
21.0	0.0775	0.136	1.305	5.022	11.91
22.0	0.0791	0.139	1.332	5.128	12.15
23.0	0.0807	0.142	1.359	5.234	12.39
24.0	0.0824	0.145	1.386	5.340	12.64
25.0	**0.0840**	**0.147**	**1.413**	**5.446**	**12.88**
26.0	0.0856	0.150	1.440	5.552	13.13
27.0	0.0873	0.153	1.467	5.658	13.37
28.0	0.0889	0.156	1.494	5.764	13.62
29.0	0.0906	0.159	1.522	5.870	13.87
30.0	0.0922	0.162	1.549	5.976	14.12

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Dissolution Testing

Dissolution testing is generally used in oral formulations with the aim of evaluating "in vitro" the dissolution of the active principles contained in the pharmaceutical form. This assay is a fundamental part of the analyses used to evaluate pharmaceutical forms during their development (to formulate the drug dosage form), stability and quality control.

In-vitro dissolution testing is a critical test that has to correlate with in-vivo clinical studies and which could require specific method developments. Dissolution testing is described in many pharmacopoeias, in EP, USP chapters and FDA guidelines.

There are **different apparatus** that can be used for this test, but a general apparatus consists of:

- a **cylindrical vessel** with precisely defined dimensions and capacities, which may be covered with a lid to retard evaporation, and made of glass or other inert, transparent material;
- a **motor**;
- a stainless steel **drive shaft** that can rotate at different speeds without significant deviations;
- a stainless steel **cylindrical basket** where to place the sample.

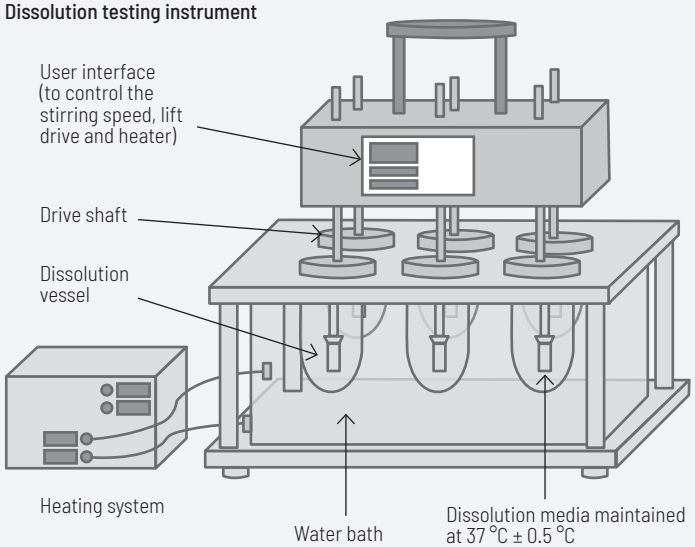
The vessel is partially immersed in a suitable water bath that allows maintaining the temperature inside the vessel at 37.0 °C ± 0.5 °C during the test.

No part of the appliance, or the area where it is installed, should produce significant movement, agitation or vibration beyond that due to the stirring element.

The device also allows to select the speed of rotation of the axes according to what is specified in the corresponding monograph and keep it within ± 4 %.

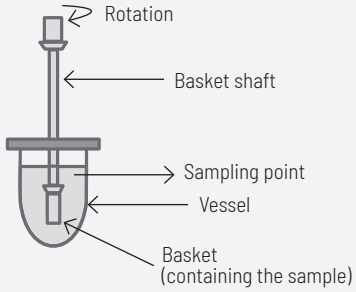
All the dimensions are well defined in the Pharmacopoeias. Also, other apparatus with some modifications from the previous one are defined.

Dissolution testing instrument

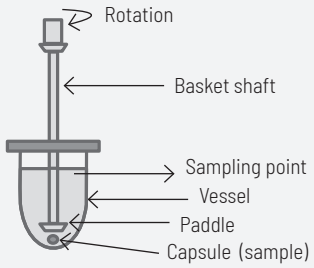


Common types of stirring elements

Basket stirring element



Paddle stirring element



The standard procedure consists of:

- Place the stated volume of the **Dissolution medium (± 1 %)** in the vessel of the apparatus.
- Assemble apparatus, equilibrate the medium to **37 °C ± 0.5 °C** and remove the thermometer.
- After equilibration, **place the dosage form** in the dry basket (take care to **exclude air bubbles** from the surface of the dosage form) or in the bottom of the vessel (if paddle stirring element is used).
- Immediately **start the rotation** of the agitation element at the speed specified in the corresponding monograph.
- After the specified time, or at each of the established times, **withdraw an aliquot** from an area at a medium distance between the surface of the medium and the upper part of the basket or the rotating vane and not less than 10 mm from the vessel wall. In some cases, it will be necessary to replace the aliquots removed for the analysis with equal volumes of media heated at 37 °C.
- Keep the **glass covered** for the duration of the test and check the temperature inside each glass at appropriate intervals.
- **Filter** and **analyse** the aliquots extracted as specified in the corresponding monograph.

The Dissolution medium depends on the type of dosage form (Immediate-Release, Extended-Release or Delayed-Release). In the following table it is summarized some of the most common dissolution media.

Dissolution media

Type of dosage form			Dissolution medium
Immediate-Release			Specified in the individual monograph
Extended-Release			Specified in the individual monograph
Delayed-Release	Method A	Acid Stage	750 mL 0.1 N HCl
		Buffer Stage	Add 250 mL 0.20 M tribasic sodium phosphate. Adjust to pH 6.8 ± 0.05 with 2 N HCl or with 2 N NaOH
	Method B	Acid Stage	750 mL 0.1 N HCl
		Buffer Stage	Drain the acid from the vessel. Add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing (3:1): 0.1 N HCl with 0.20 M tribasic sodium phosphate. Adjust to pH 6.8 ± 0.05 with 2 N HCl or with 2 N NaOH
For dosage forms containing or coated with gelatine			
Dissolution Medium with pH ≤ 4.0			Pepsin that results in an activity of NMT 750,000 Units/L of dissolution medium
Dissolution Medium with pH > 4.0 and < 6.8			Papain that results in an activity of NMT 550,000 Units/L of dissolution medium
			Bromelain that results in an activity of NMT 30 gelatine-digesting units (GDU)/L of dissolution medium
Dissolution Medium with pH ≥ 6.8			Pancreatin that results in an activity of NMT 2000 Units/L of dissolution medium

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Product name	Code	Package
Bromelain from pineapple stem BioChemica	A1548,0025	25 g
	A1548,0500	500 g
Hydrochloric Acid 0.1 mol/l (0.1N) volumetric solution	181023.1211	1000 mL
	181023.1212	2.5 L
	181023.1214	5 L
	181023.0715	10 L
	181023.1315	10 L
Hydrochloric Acid 0.5 mol/l (0.5N) volumetric solution	181022.1211	1000 mL
	181022.1214	5 L
	181022.1315	10 L
Hydrochloric Acid 2 mol/l (2N) volumetric solution	182108.1211	1000 mL
	182108.0716	25 L
Pancreatin	A0585,0100	100 g
	A0585,0500	500 g
Papain	A3824,0025	25 g
Pepsin	A4289,0025	25 g
	A4289,0100	100 g
Pepsin 1:10.000 NF	175208.0011	1000 g
SDS for analysis, ACS	132363.1207	50 g
	132363.1209	250 g
	132363.0914	5 kg
di-Sodium Hydrogen Phosphate anhydrous (Reag. Ph. Eur.) for analysis, ACS	131679.1210	500 g
	131679.1211	1000 g
	131679.0914	5 kg
	131679.0416	25 kg
Sodium Hydroxide 2 mol/l (2N) volumetric solution	182158.1211	1000 mL
Sulfuric Acid 0.05 mol/l (0.1N) volumetric solution	181061.1211	1000 mL
	181061.1214	5 L
	181061.1315	10 L
	181061.0716	25 L

Package pictograms

	Glass bottle	PP	Plastic bucket
P	Plastic bottle		Sol-Pack: Plastic container in a carton box (cubitainer), with tap
P	Plastic jerrycan		Paperboard box

A195-1,EN;201805

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