Water

1 Nonproprietary Names

BP: Purified water
JP: Purified water
PhEur: Aqua purificata
USP: Purified water
See also Sections 8 and 17.

2 Synonyms

Aqua; hydrogen oxide.

3 Chemical Name and CAS Registry Number

Water [7732-18-5]

4 Empirical Formula

H_2O

Molecular Weight

18.02

5 Structural Formula

H_2O

6 Functional Category

Solvent.

7 Applications in Pharmaceutical Formulation or Technology

Water is the most widely used excipient in pharmaceutical production operations. Specific grades of water are used for particular applications in concentrations up to 100%; *see* Table I. Purified water and water for injection are also used for cleaning operations during production of pharmaceutical products.

8 Description

The term 'water' is used to describe potable water that is freshly drawn direct from the public supply and is suitable for drinking. The chemical composition of potable water is variable and the nature and concentrations of the impurities in it depend upon the source from which it is drawn. Although potable water must be both palatable and safe to drink, for most pharmaceutical applications potable water is purified by distillation, ion exchange treatment, reverse osmosis, or some other suitable process to produce 'purified water'. For certain applications, water with pharmacopeial specifications differing from those of purified water should be used, e.g., water for injection; *see* Sections 9 and 18.

Water is a clear, colorless, odorless, and tasteless liquid.

Table I: Typical applications of specific grades of water.

Type	Use
Bacteriostatic water for injection	Diluent for ophthalmic and multiple-dose injections.
Potable water	Public supply suitable for drinking, the purity of which is unlikely to be suitable for use in the manufacture of pharmaceuticals.
Purified water	Vehicle and solvent for the manufacture of drug products and pharmaceutical preparations; not suitable for use in the manufacture of parenteral products.
Sterile water for inhalation	Diluent for inhalation therapy products.
Sterile water for injection	Diluent for injections.
Sterile water for irrigation	Diluent for internal irrigation therapy products.
Water for injections in bulk	Water for the bulk preparation of medicines for parenteral administration.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point: 100°C
Critical pressure: 22.1 MPa (218.3 atm)
Critical temperature: 374.2°C
Dielectric constant: $D^{25} = 78.54$
Dipole moment:
1.76 in benzene at 25°C
1.86 in dioxane at 25°C
Ionization constant: 1.008×10^{-14} at 25°C.
Latent heat of fusion: 6 kJ/mol (1.436 kcal/mol)
Latent heat of vaporization: 40.7 kJ/mol (9.717 kcal/mol)
Melting point: 0°C
Refractive index: $n_D^{20} = 1.3330$
Solubility: miscible with most polar solvents.
Specific gravity: 0.9971 at 25°C.
Specific heat (liquid): 4.184 J/g/°C (1.00 cal/g/°C) at 14°C.
Surface tension: 71.97 mN/m (71.97 dynes/cm) at 25°C.
Vapor pressure: 3.17 kPa (23.76 mmHg) at 25°C.
Viscosity (dynamic): 0.89 mPa s (0.89 cP) at 25°C.

11 Stability and Storage Conditions

Water is chemically stable in all physical states (ice, liquid, and vapor). Water for specific purposes should be stored in appropriate containers; *see* Table III.

Table II: Pharmacopeial specifications of water for different pharmaceutical applications.

Test	Water JP 2001	Purified water JP 2001	Purified water in bulk PhEur 2002	Purified water in containers PhEur 2002	Purified water USP 25	Water, highly purified PhEur 2002	Sterile water for injection USP 25	Bacteriostatic water for injection USP 25	Sterile water for inhalation USP 25	Sterile water for irrigation USP 25	Sterile purified water USP 25	Water for injection[a] JP 2001	Water for injection USP 25	Water for injection (in bulk) PhEur 2002	Sterile water for injection PhEur 2002	Sterile purified water JP 2001
Identification	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Production	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–
Characters	+	+	–	+	–	+	–	–	–	–	–	–	–	+	–	+
Appearance of solution	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Odor and taste	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+
pH	5.8–8.6	–	–	–	–	–	5.0–7.0	4.5–7.0	4.5–7.5	5.0–7.0	5.0–7.0	–	5.0–7.0	–	–	–
Acid or alkali	–	+	–	+	–	–	–	–	–	–	–	+	–	–	+	+
Cadmium	⩽0.01 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Chloride	⩽200 mg/L	+	–	+	–	–	+	–	+	+	+	+	+	–	+	+
Cyanide	⩽0.01 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Copper	⩽1 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sulfate	–	+	–	+	–	–	+	+	+	+	+	+	+	–	–	+
Ammonium	⩽0.05 mg/L	⩽0.05 mg/L	–	+	–	–	+	–	+	+	+	+	+	–	–	⩽0.05 mg/L
Iron	⩽0.3 ppm	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Calcium	–	–	–	+	–	–	+	+	+	+	+	–	+	–	–	–
Lead	⩽0.1 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Magnesium	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Aluminum	–	–	⩽10 µg/L	–	–	⩽10 µg/L	–	–	–	–	–	–	–	–	–	–
Nitrate	–	–	⩽0.2 ppm	–	–	⩽0.2 ppm	–	–	–	–	–	+	–	–	+	+
Nitrogen from nitrate	⩽10 mg/L	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nitrogen from nitrite	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Carbon dioxide	–	–	–	–	–	–	+	+	+	+	+	–	+	–	–	–
Heavy metals	⩽1 mg/L	+	⩽0.1 ppm	+	–	⩽0.1 ppm	–	–	–	–	–	+	–	–	+	+
Oxidizable substances	–	–	–	+	–	–	+	–	+	+	+	–	+	–	+	–
Potassium permanganate-reducing substances	⩽10 mg/L	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Residue on evaporation	⩽500 mg/L	⩽1.0 mg	–	⩽0.001%	–	–	–	–	–	–	–	+	–	–	+	⩽1.0 mg
Total organic carbon	–	–	–	–	+	–	–	–	–	–	–	+[b]	–	–	+	–
Total hardness	⩽300 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Conductivity	–	–	–	–	+	–	–	–	–	–	–	–	–	–	⩽25 µS/cm	–
Anionic surfactants	⩽0.5 mg/L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Antimicrobial agents	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sterility	–	–	–	–	–	–	+	+	+	+	+	+	+	–	–	+
Particulate matter	–	–	–	–	–	–	+	+	–	–	–	–	–	–	+	–
Microbial contamination	+	–	–	⩽10^2/mL	–	–	–	–	–	–	–	–	–	–	–	–
Bacterial endotoxins	–	–	⩽0.25 IU/mL	⩽0.25 IU/mL	–	⩽0.25 IU/mL	⩽0.25 EU/mL	⩽0.5 EU/mL	⩽0.5 EU/mL	⩽0.25 EU/mL	–	⩽0.25 EU/mL	⩽0.25 EU/mL	⩽0.25 IU/mL	0.25 IU/mL	–

[a] For water for injection preserved in containers and sterilized, the JP 2001 provides separate tests for acid or alkali, chloride, ammonium, and residue on evaporation within the monograph.

[b] For water for injection prepared by reverse osmosis–ultrafiltration.

Table III: Storage requirements for different grades of water.

Type	Storage requirements[a]
Bacteriostatic water for injection	Preserve in single-dose and multiple-dose containers, preferably of Type I or Type II glass, not larger than 30 mL in size.
Potable water	Preserve in tightly sealed containers.
Purified water	Preserve in tightly sealed containers. If it is stored in bulk, the conditions of storage should be designed to limit the growth of microorganisms and avoid any other contamination.
Sterile water for inhalation	Preserve in single-dose containers, preferably of Type I or Type II glass.
Sterile water for injection	Preserve in single-dose containers, preferably of Type I or Type II glass, not more than 1000 mL in size.
Water for injection	Preserve in tightly sealed containers.
Water for injections in bulk	Collect and store in conditions designed to prevent growth of microorganisms and avoid any other contamination.

[a] To prevent evaporation and to maintain quality.

12 Incompatibilities

In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures.

Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions, and with certain organic materials and calcium carbide.

13 Method of Manufacture

Unlike other excipients, water is not purchased from outside suppliers but is manufactured in-house by pharmaceutical companies. The selection of the most appropriate system and the overall design of the system are crucial factors to ensure that water of the correct quality is produced.[1,2]

To produce potable or drinking water, insoluble matter is first removed from a water supply by coagulation, settling, and filtering processes. Pathogenic microorganisms present are then destroyed by aeration, chlorination, or some other means. Water may also be rendered free of viable pathogenic microorganisms by active boiling for 15–20 minutes. Finally, the palatability of the water is improved by aeration and charcoal filtration.

The quality attributes of water for injection (WFI) are stricter than for purified water. Consequently, the preparation methods typically vary in the last stage to ensure good control of quality of WFI. Methods for the production of WFI are the subject of current debate. The PhEur 2002 indicates that only distillation would give assurance of consistent supply of the appropriate quality. However, the PhEur 2002 permits distillation, ion exchange, or any other suitable method that complies with regulations on water intended for human consumption laid down by the competent authority.

The USP 25 and the JP 2001 permit the use of reverse osmosis (RO) in addition to distillation and ultrafiltration. Purified water suitable for use in pharmaceutical formulations is usually prepared by purifying potable water by one of several processes, such as distillation; deionization; or reverse osmosis.[1,3–8]

Distillation

A wide variety of stills are available to produce purified or distilled water. A typical design consists of an evaporator, vapor separator, and compressor. The distilland (raw feed water) is heated in the evaporator to boiling and the vapor produced is separated from entrained distilland in the separator. The vapor then enters a compressor where the temperature of the vapors is raised to 107°C. Superheated vapors are then condensed on the outer surface of the tubes of the evaporator containing cool distilland circulating within.

Vapor compression stills of various sizes are commercially available and can be used to produce water of high purity when properly constructed. A high-quality distillate, such as water for injection, can be obtained if the water is first deionized. The best stills are constructed of types 304 or 316 stainless steel and coated with pure tin, or are made from chemical-resistant glass.

De-ionization

Cationic and anionic ion exchange resins are used to purify potable water by removing any dissolved ions. Dissolved gases are also removed, while chlorine, in the concentrations generally found in potable water, is destroyed by the resin itself. Some organics and colloidal particles are removed by adsorption and filtration. Resin beds may, however, foster microbial life and produce pyrogenic effluent unless adequate precautions are taken to prevent contamination. Mixed-bed units produce purer water (lower conductivity) than do stills. However, the organic matter content is usually higher. Ion exchange units are normally used today to treat raw feed water prior to distillation or reverse osmosis processing.

Reverse osmosis

Water is forced through a semipermeable membrane in the opposite direction to normal osmotic diffusion. A very small proportion of inorganic salts passes through, but undissolved materials (bacteria and large molecules such as viruses, pyrogens, and high-molecular-weight organics) are removed.

Ultrafiltration

A permeable membrane is used for mechanical separation. Impurities including endotoxins are removed by the membrane.

14 Safety

Water is the base for many biological life forms, and its safety in pharmaceutical formulations is unquestioned provided it meets standards of quality for potability[9] and microbial content; *see* Sections 9 and 18. Plain water is considered slightly more toxic upon injection into laboratory animals than physiological salt solutions such as normal saline or Ringer's solution.

Ingestion of excessive quantities of water can lead to water intoxication, with disturbances of the electrolyte balance.

Water for injection should be free from pyrogens.

LD_{50} (mouse, IP): 25 g/kg[10]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in nonparenteral and parenteral medicines licensed in the UK and USA.

17 Related Substances

Bacteriostatic water for injection; carbon dioxide-free water; de-aerated water; hard water; soft water; sterile water for inhalation; sterile water for injection; sterile water for irrigation; water for injection.

Bacteriostatic water for injection

Comments: the USP 25 describes bacteriostatic water for injection as sterile water for injection that contains one or more suitable antimicrobial agents.

Carbon dioxide-free water

Comments: purified water that has been boiled vigorously for 5 minutes and allowed to cool while protecting it from absorption of atmospheric carbon dioxide.

De-aerated water

Comments: purified water that has been boiled vigorously for 5 minutes and cooled to reduce the air (oxygen) content.

Hard water

Comments: water containing the equivalent of not less than 120 mg/L and not more than 180 mg/L of calcium carbonate.

Soft water

Comments: water containing the equivalent of not more than 60 mg/L of calcium carbonate.

Sterile water for inhalation

Comments: the USP 25 describes sterile water for inhalation as water purified by distillation or by reverse osmosis and rendered sterile. It contains no antimicrobial agents or other added substances, except where used in humidifiers or other similar devices, and where liable to contamination over a period of time.

Sterile water for injection

Comments: the USP 25 describes sterile water for injection as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Sterile water for irrigation

Comments: the USP 25 describes sterile water for irrigation as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Water for injection

Comments: the USP 25 describes water for injection as water purified by distillation or reverse osmosis. It contains no added substances. The PhEur 2002 title is 'water for injections' and comprises two parts: 'water for injections in bulk' and 'sterilized water for injection.' The PhEur 2002 states that water for injections is produced by distillation.

18 Comments

In most pharmacopeias, the term 'water' now refers to purified or distilled water.

Without further purification, 'water' may be unsuitable for certain pharmaceutical applications; for example, the presence of calcium in water affects the viscosity and gel strength of algins and pectin dispersions, while the use of potable water affects the clarity and quality of cough mixtures, and the stability of antibiotic liquid preparations.

Water commonly contains salts of aluminum, calcium, iron, magnesium, potassium, sodium, and zinc. Toxic substances such as arsenic, barium, cadmium, chromium, cyanide, lead, mercury, and selenium may constitute a danger to health if present in excessive amounts. Ingestion of water containing high amounts of calcium and nitrate is also contraindicated. National standards generally specify the maximum limits for these inorganic substances in potable water. Limits have also been placed on microorganisms, detergents, phenolics, chlorinated phenolics, and other organic substances. The WHO[11] and national bodies have issued guidelines for water quality, although many countries have their own standards for water quality embodied in specific legislation.[12] *See* Table IV.

Control of microbiological contamination is critical for waters used in preparation of pharmaceuticals as proliferation of microorganisms can potentially occur during all stages of manufacture, storage, or distribution. Suitable control is achieved by ensuring that the water system is well designed and well maintained. Purified water that is produced, stored, and circulated at ambient temperatures is susceptible to the establishment of biofilms; therefore, frequent monitoring, high usage, correct flow rate, and appropriate sanitization are all factors that require consideration to ensure that water is satisfactory.[13]

Table IV: Limits for inorganic substances in potable water (mg/L).

Contaminant	UK (mg/L)	WHO (mg/L)
Aluminum	0.2	0.2
Ammonium	0.5	—
Antimony	0.01	—
Arsenic	0.05	0.05
Barium	1.0	No limit
Beryllium	—	No limit
Boron	2.0	—
Cadmium	0.005	0.005
Calcium	250	—
Chloride	400	250
Chromium	0.05	0.05
Copper	3.0	1.0
Cyanide	0.05	0.1
Fluoride	1.5	1.5
Iron	0.2	0.3
Lead	0.05	0.05
Magnesium	50	—
Manganese	0.05	0.1
Mercury	0.001	0.001
Nickel	0.05	No limit
Nitrate (as N)	—	10
Nitrate (as NO_3)	50	—
Nitrite (as NO_2)	0.1	—
Phosphorus	2.2	—
Potassium	12	—
Selenium	0.01	0.01
Silver	0.01	No limit
Sodium	150	200
Sulfate	250	400
Zinc	5.0	5.0

Monitoring of the whole system is essential in order to demonstrate that correct microbiological quality is achieved. For WFI the recommended methodology is membrane filtration (0.45μm) as a large sample size (100–300 mL) is required. For purified water, membrane filtration or plate count methods are typically used depending on the quality requirements of the system. It is important to set appropriate target, alert, and action limits to serve as an indication of action required to bring the quality of water back under control. It is recognized that limits are not intended as pass/fail criteria for water or product batches; however, an investigation regarding the implications should be conducted.[14]

Validation is conducted to provide a high level of assurance that the water production and distribution system will consistently produce water conforming to a defined quality specification. The validation process serves to qualify the design (DQ), installation (IQ), operation (OQ), and performance (PQ) of the system. The extent of monitoring data required should be defined, with consideration given to whether validation to FDA guidelines is required.[14] It is also important to have an ongoing control program with respect to maintenance and periodic reviews of the performance of the water system.

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