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A REVIEW ON WATER USED IN PHARMA INDUSTRY

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ABSTRACT

Water is a key ingredient used in many pharmaceutical and life sciences operations. Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, active pharmaceuticalingredients (APIs) and intermediates. Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Water can be used in a variety of applications, some requiringextreme microbiological control and others requiring none. Pharmaceutical water production, storage and distribution systemsshould be designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriatequality. It is necessary to validate the water production process to ensure the water generated, stored and distributed is not beyondthe designed capacity and meets its specifications.

KEYWORDS: Drinking water, water for injection, Water storage and distribution system, Water Treatment.

INTRODUCTION

Water[4]

Water is a transparent and nearly colorless chemical substance that is the main constituent of Earth's streams, lakes, and oceans, and the fluids of most living organisms. Its chemical formula is $\mathbf{H_2O}$, meaning that its molecule contains one oxygen and two hydrogen atoms, that are connected by covalent bonds. Water strictly refers to the liquid state of that substance, that prevails at standard ambient temperature and pressure; but it often refers also to its solid state (ice) or its gaseous state (steam or water vapor). It also occurs in nature as snow, glaciers, ice packs and icebergs, clouds, fog, dew, aquifers, and atmospheric humidity. Water covers 71% of the Earth's surface. Water on Earth moves continually through the water cycle of evaporation and transpiration (evapotranspiration), condensation, precipitation, and runoff, usually reaching the sea. Safe drinking water is essential to humans and other life forms even though it provides no calories or organic nutrients. Large quantities of water, ice, and steam are used for cooling and heating, in industry and homes. Water is a good solvent for a wide variety of chemical substances; as such it is widely used in industrial processes, and in cooking and washing.

Sources of Water[2]

Surface water

Surface water is water in a river, lake or fresh water wetland. Although the only natural input to any surface water system is precipitation within its watershed, the total quantity of water in that system at any given time is also dependent on many other factors. These factors include storage capacity in lakes, wetlands and artificial reservoirs, the permeability of the soil beneath these storage bodies, the runoff characteristics of the land in the watershed, the timing of the precipitation and local evaporation rates.

Ground water

Groundwater is fresh water located in the subsurface pore space of soil and rocks. It is also water that is flowing withinaquifers below the water table. Sometimes it is useful to make a distinction between groundwater that is closely associated with surface water and deep groundwater in an aquifer (sometimes called "fossil water"). Groundwater can be thought of in the same terms as surface water: inputs, outputs and storage. The critical difference is that due to its slow rate of turnover, groundwater storage is generally much larger (in volume) compared to inputs than it is for surface water.

Frozen water

Several schemes have been proposed to make use of icebergs as a water source, however to date this has only been done for research purposes. Glacier runoff is considered to be surface water.

Ten of Asia's largest rivers flow from there, and more than a billion people's livelihoods depend on them. To complicate matters, temperatures there are rising more rapidly than the global average.

Water and tid
Sea water contains about 3.5% salt on average, plus smaller amounts of other substances. The physical properties of sea water differ from fresh water in some important respects. It freezes at a lower temperature (about −1.9 °C) and its density increases with decreasing temperature to the freezing point, instead of reaching maximum density at a temperature above freezing. The salinity of water in major seas varies from about 0.7% in the Baltic Sea to 4.0% in the Red Sea.

Upland lakes and reservoirs
Typically located in the headwaters of river systems, upland reservoirs are usually sited above any human habitation and may be surrounded by a protective zone to restrict the opportunities for contamination. Bacteria and pathogen levels are usually low, but some bacteria, protozoa or algae will be present. Where uplands are forested or peaty, humic acids can color the water. Many upland sources have low pH which requires adjustment.

Rivers, canals and low land reservoirs
Low land surface waters will have a significant bacterial load and may also contain algae, suspended solids and a variety of dissolved constituents. Atmospheric water generation is a new technology that can provide high quality drinking water by extracting water from the air by cooling the air and thus condensing water vapor.

Chemical Compound-Water is a polar inorganic compound that is at room temperature a tasteless and odorless liquid, nearly colorless with a hint of blue.
Density: 1 g/cm³
Boiling point: 100 °C
Formula: H_2O
Melting point: 0 °C
IUPAC ID: Water, Oxidane

Physical–Chemical Factors[20]
The chemical, physical, and biological compatibilityof the two kinds of waters must beinvestigated, as these properties can greatlyinfluence plugging of the aquifer and thereforethe rate and duration of recharge.

1. Physical Characteristics
The main physical characteristics to considerare:
1) pH,
2) Temperature,
3) Electrical Conductivity,
4) Total Dissolved Solids,
5) Color and Odor

Affects water viscosity, as thetwo properties are inversely proportional. Sincethe hydraulic conductivity of the ground isinversely proportional to water viscosity, thismeans that water that is cold flows more slowlyin the aquifer than warmer water. Moreover, iftemperature decreases water density growsproportionally, leading to thermal stratificationof water in the aquifer. This stratification lead tothe obstruction of pores and reduces waterinfiltration into the aquifer.

2. Chemical Characteristics
The main important parameters affectingartificial recharge are dissolved gas anddissolved salts. Dissolved or suspended gas (air) has a doublefunction—chemical and physical—inside theaquifer. The presence of small air bubblesinside the pores may cause blockage of theaquifer and reduce percolation into theunsaturated zone. Oxygen in the air causesredox reactions in the ground that canchemically precipitate compounds that blockthe aquifer, reducing water quality. Oxidation can destroy pathogenic organisms, prevent the leaching of iron and manganese, and cause the precipitation of iron salts ingroundwater. The redox reactions raise the iron content ofthe water by increasing the solubility of theiron.

The five main properties of water
1. Its attraction to polar molecules
2. High-specific heat
3. High heat of vaporization
4. The lower density of ice
5. High polarity

A) Test and Odour
Pure water is usually described as tasteless and odorless, although humans have specific sensors that can feel the presence of water in their mouths, and frogs are known to be able to smell it. Humansand other animals have developed senses that enable them to evaluate the potability of water by avoiding water.

B) Color and appearance
The apparent color of natural bodies of water (and swimming pools) is often determined more by dissolved and suspended solids, or by reflection of the sky, than by water itself. Light in the visible electromagnetic spectrum can traverse a couple meters of pure water (or ice) without significant absorption, so that it looks transparent and colorless.[18] Thus aquatic plants, algae, and other photosynthetic organisms can live in water up to hundreds of meters deep, because sunlight can reach them.

Water cycle
The water cycle (known scientifically as the hydrologic cycle) refers to the continuous exchange of water within the hydrosphere, between the atmosphere, soil water, surface water, groundwater, and Water moves perpetually through each of these regions in the water cycle consisting of following transfer processes:
- Evaporation from oceans and other water bodies into the air and transpirationfrom land plants and animals into air.
- Precipitation, from water vapor condensing from the air and falling to earth or ocean.
- Run Off from the land usually reaching the sea.

Most water vapor over the oceans returns to the oceans, but winds carry water vapor over land at the same rate as runoff into the sea, about 47 Tt per year. Over land, evaporation and transpiration contribute another 72 Tt per year. Precipitation, at a rate of 119 Tt per year over land, has several forms: most commonly rain, snow, and hail, with some contribution from fog and dew. Dew is small drops of water that are condensed when a high density of water vapor meets a cool surface

WATER FOR PHARMACEUTICAL INDUSTRY PURPOSES[19]

Water is one of the most commonly used substances, vehicle, raw materials, or an ingredient in the production, formulation, and processing of pharmaceuticals and also in the cleaning of manufacturing equipment's. Control of the inorganic, organic impurities and microbiological quality of water is important because propagationof micro-organism is ubiquitous in water and it may occur during the, distribution, refinement and storage of water.

Major differences among these grades of water consist of the following quality attributes

- Microbial counts
- Endotoxin, which is due to the presence of microbes
- Organic and inorganic impurities

The USP identifies several grades of water that are acceptable for use in pharmaceuticals, and also defines the quality attributes for the manufacturing of pharmaceuticals according to its criticality as

1. Potable water
2. Purified water
3. Water for injection
4. Sterile water for injection
5. Sterile water for inhalation
6. Sterile water for irrigation
7. Sterile bacteriostatic water for injection

"Water for injection (WFI) is the most purified water, and careful attention should be paid to the validation of its manufacturing process.

Water in industry

The water industry provides drinking water and wastewater services (including sewage treatment) to households and industry. Water supply facilities include water wells, cisternsfor rainwater harvesting, water supply networks, and water purification facilities, water tanks,water towers, water pipes including old aqueducts. Atmospheric water generators are in development.

Drinking water is often collected at springs, extracted from artificial borings (wells) in the ground, or pumped from lakes and rivers. Water may require purification for human consumption. This may involve removal of undissolved substances, dissolved substances and harmful microbes More advanced techniques exist, such as reverse osmosis. Desalination of abundant seawater is a more expensive solution used in coastal arid climates. The distribution of drinking water is done through municipal water systems, tanker delivery or as bottled water. Governments in many countries have programs to distribute water to the needy at no charge. Reducing usage by using drinking (potable) water only for human consumption is another option.

Water storage and distribution system[1]

The storage and distribution system should be considered as a key part of the whole system and should be designed to be fully integrated with the water purification components of the system. Water is one of the major commodities used by the pharmaceutical industry. It may be present as an excipient or used for reconstitution of the products during synthesis, production of the finished product or as cleaning agent for rinsing vessels, equipment, primary packaging materials etc.

Water shortage, industrial wastewater treatmentand environmental engineering techniques[17]

Water shortage is an immense hurdle to the progress of human mankind. Global water shortage, industrialwastewater treatment and the holistic hurdles toeconomic growth are the negative issues to the progressof human civilization. The frontiers of challengesare wide and visionary. Effort, direction and futurestrategies will go a long way in evolving a new generationof scientific hope and immense optimism.

Global water shortage and new generation technologies[17]

Global water shortage and application of new generationenvironmental engineering tools are ushering in a newvision in the domain of technological validation. Thetarget of our present scientific generation is to delve deepinto the unknown and unravel the hidden truths ofenvironmental engineering techniques. Global watershortage is in a deep and unfathomable crisis.

Softeners

Water softeners may be located either upstream or downstream of disinfectant removal units. They utilize sodium-based cation-exchange resins to remove water-hardness ions, such as calcium and magnesium, that could foul or interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization devices, and distillation units Water softener resin beds are regenerated with concentrated sodium chloride solution (brine).

Disinfection[18]

An overarching goal for providing safe water is affordably androbustly to disinfect water from traditional and emerging pathogens, without creating more problems due to the disinfection process itself.

Decontamination[18]

The overarching goal for the future of decontamination is to detectand remove toxic substances from water affordably and robustly. Widely distributed substances, such as arsenic, heavy metals, halogenatedaromatics, nitrosoamines, nitrates, phosphates, and so onare known to cause harm to humans and the environment. Two keyproblems are that the amount of suspected harmful agents is growingrapidly, and that many of these compounds are toxic in trace quantities.

Industrial applications

Water is used in power generation. Hydroelectricity is electricity obtained from hydropower. Hydroelectric power comes from water driving a water turbine connected to a generator. Hydroelectricity is a low-cost, non-polluting, renewable energy source. The energy is supplied by the motion of water. Pressurized water is used in water blasting and water jet cutters. Also, very high pressure water guns are used for precise cutting. It works very well, is relatively safe, and is not harmful to the environment. It is also used in the cooling of machinery to prevent overheating, or prevent saw blades from overheating.

Application of specific waters to processes and dosage forms[15]

Product licensing authorities define the requirement to use the specificgrades of WPU for different dosage forms or for different stagesin washing, preparation, synthesis, manufacturing or formulation. The grade of water used should take into account the nature andintended use of the intermediate or finished product and the stage inthe manufacturing process at which the water is used.

Water Treatment[2]

Water treatment, however, can also be organized or categorized by the nature of the treatment process operation being used; for example, physical, chemical or biological. Examples of these treatment steps are shown below. A complete treatment system may consist of the application of a number of physical, chemical and biological processes to the water. Some Physical, Chemical and Biological water Treatment Methods.

1) Physical

a. Sedimentation (Clarification), b. Screening, c. Aeration, d. Filtration, e. Flotation and Skimming, f. Degasification, g. Equalization

2) Chemical

a. Chlorination, b. Ozonation, c. Neutralization, d. Coagulation, e. Adsorption f. Ion Exchange

3) Biological

a. Aerobic, b. Activated Sludge Treatment Method, c. Trickling Filtration, d. Oxidation Ponds, e. Lagoons, f. Aerobic Digestion, g. Anaerobic Digestion, h. Septic Tanks, i. Lagoons.

Water treatment process

1) Physical methods

These include processes where no gross chemical or biological changes are carried out and strictly physical phenomena are used to improve or treat the water. Examples would be coarse screening to remove larger entrained objects and sedimentation (or clarification).

a) Coagulation and flocculation

One of the first steps in a conventional water purification process is the addition of chemicals to assist in the removal of particles suspended in water. Particles can be inorganic such as clay and silt or organic such as algae, bacteria, viruses, protozoa and natural organic matter. Inorganic and organic particles contribute to the turbidity and color of water.

b) Sedimentation

In the process of sedimentation, physical phenomena relating to the settling of solids by gravity are allowed to operate. Usually this consists of simply holding the water for a short period of time in a tank under quiescent conditions, allowing the heavier solids to settle, and removing the "clarified" effluent.

c) Aeration

Another physical treatment process consists of aeration that is, physically adding air, usually to provide oxygen to the water.

d) Filtration

After separating most floc, the water is filtered as the final step to remove remaining suspended particles and unsettled floc.

Rapid sand filters

The most common type of filter is a rapid sand filter. Water moves vertically through sand which often has a layer of activated carbon or anthracite coal above the sand. The top layer removes organic compounds, which contribute to taste and odor.

Advantages

- Filters out much smaller particles than paper and sand filters can.
- Filters out virtually all particles larger than their specified pore sizes.
- They are quite thin and so liquids flow through them fairly rapidly.
- They are reasonably strong and so can withstand pressure differences across them of typically 2–5 atmospheres.
- They can be cleaned (back flushed) and reused
- Slow sand filters

Membrane filtration

Membrane filters are widely used for filtering both drinking water and sewage. For drinking water, membrane filters can remove virtually all particles larger than 0.2 um—including giardia and cryptosporidium.

2) Chemical treatment
It consists of using some chemical reaction or reactions to improve the water quality. Probably the most commonly used chemical process is chlorination.

a) Chlorination
The most common disinfection method involves some form of chlorine or its compounds such as chloramine or chlorine dioxide. Chlorine is a strong oxidant that rapidly kills many harmful micro-organisms. Because chlorine is a toxic gas, there is a danger of a release associated with its use.

b) Ozone disinfection
Ozone is an unstable molecule which readily gives up one atom of oxygen providing a powerful oxidizing agent which is toxic to most waterborne organisms. It is an effective method to inactivate harmful protozoa that form cysts.

c) Neutralization
A chemical process commonly used in many industrial water treatment operations is neutralization. Neutralization consists of the addition of acid or base to adjust pH levels back to neutrality. Since lime is a base it is sometimes used in the neutralization of acid wastes.

d) Coagulation
Coagulation consists of the addition of a chemical that, through a chemical reaction, forms an insoluble end product that serves to remove substances fromthe waste water. Polyvalent metals are commonly used as coagulating chemicals in water treatment and typical coagulants would include lime (that can also be used in neutralization), certain iron containing compounds (such as ferric chloride or ferric sulfate) and alum (aluminum sulfate).

3) Biological treatment methods
This method uses microorganisms, mostly bacteria, in the biochemical decomposition of wastewaters to stable end products. Generally, biological treatment methods can be divided into aerobic and anaerobic methods, based on availability of dissolved oxygen. While the devices used in wastewater treatment are numerous and will probably combine physical, chemical and biological methods, they may all be generally grouped under six methods:

1. Preliminary Treatment,
2. Primary Treatment,
3. Secondary Treatment,
4. Disinfection,
5. Sludge Treatment,
6. Tertiary Treatment

Preliminary Treatment
At most plants preliminary treatment is used to protect pumping equipment and facilitate subsequent treatment processes. To affect the objectives of preliminary treatment, the following devices are commonly used:
1. Screens -- rack, bar or fine,
2. Comminuting devices -- grinders, cutters, shredders,
3. Grit chambers,
4. Pre-aeration tanks.

Primary Treatment
In this treatment, most of the settleable solids are separated or removed from the wastewater by the physical process of sedimentation. Because of variations in design, operation, and application, settling tanks can be divided into four general groups:
1. Septic tanks
2. Two story tanks -- Imhoff and several proprietary or patented units
3. Plain sedimentation tank with mechanical sludge removal
4. Upward flow clarifiers with mechanical sludge removal

When chemicals are used, other auxiliary units are employed. These are
1. Chemical feed units,
2. Mixing devices,
3. Flocculators

Secondary Treatment
Secondary treatment depends primarily upon aerobic organisms which biochemically decompose the organic solids to inorganic or stable organic solids. The devices used in secondary treatment may be divided into four groups:
1. Trickling filters with secondary settling tanks.
2. Activated sludge and modifications with final settling tanks.
3. Intermittent sand filters.
4. Stabilization ponds.

Chlorination
This is a method of treatment which has been employed for many purposes in all stages in wastewater treatment, and even prior to preliminary treatment. It involves the application of chlorine to the wastewater for the following purposes:
1. Disinfection or destruction of pathogenic organisms
2. Prevention of wastewater decomposition

(a) odor control, (b) protection of plant structures

3. Aid in plant operation
(a) sedimentation, (b) tricklingfilters, (c)activated sludge bulking.

4. Reduction or delay of biochemical oxygen demand (BOD).

Sludge Treatment
The solids removed from water in both primary and secondary treatment units, together with the water

removed with them, constitute water sludge. It is generally necessary to subject sludge to some treatment to prepare or condition it for ultimate disposal. Such treatment has two objectives -- the removal of part or all of the water in the sludge to reduce its volume, and the decomposition of the putrescible organic solids to mineral solids or to relatively stable organic solids. This is accomplished by a combination of two or more of the following methods:

1. Thickening,
2. Digestion with or without heat,
4. Drying on sand bed -- open or covered
5. Conditioning with chemicals,
6. Elutriation,
7. Vacuum filtration,
8. Heat drying,
9. Incineration,
10. Wet oxidation,
11. Centrifuging

Tertiary and Advanced Waste water Treatment

This merely indicates the use of intermittent sand filters for increased removal of suspended solids from the wastewater. In other cases, tertiary treatment has been used to describe processes which remove plant nutrients, primarily nitrogen and phosphorous, from wastewater.

TYPES OF WATER[1,22]

1) Hard water

Hard water is created due to acidic rain. The rain dissolves rocks into the water and hard water is created. Hard water comes from the ground and is usually taken from a well or a spring. The water is purified by passing over rocks and picking minerals up from them, such as lime, magnesium and calcium, which is why it has such a high mineral content. It is the high mineral content that is the reason for its better taste, and it is even said to be better for your health too, as the National Research Council explains that is can be used as a dietary supplement for those minerals such as calcium and magnesium.

2) Soft water

Soft water is collected from the surface, such as lakes, rivers and rainwater that has been collected. Soft water is typically high in sodium but unlike hard water, it has a small concentration of calcium and magnesium. It is due to the difference in mineral content that makes soft water better for your skin, as the minerals do not dry it up.

A) Drinking water

Drinking water can be referred as Potable Water. Drinking water must comply with the quality attributes of either the NPDWR, or the drinking water regulations of the European Union or Japan, or the WHO Drinking Water Guidelines. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well) or a combination of these sources

Production

Drinking water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce drinking-water from a specific raw water source. Typical processes employed at a user plant or by a water supply authority include

– Desalinization.
– Filtration.
– Softening.
– Disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection).
– Iron (ferrous) removal.
– Precipitation.
– Reduction of concentration of specific inorganic and/or organic materials.

The drinking water quality should be monitored routinely to account for environmental, seasonal or supply changes which have an impact on the source water quality. Equipment and systems used to produce drinking water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, and should allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained or flushed and sanitized. Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back flushing, chemical and/or thermal sanitization and frequent regeneration should be considered as appropriate.

B) Purified Water

Purified Water is used as an excipient in the production of non-parenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment's and non-parenteral product-contact components. Purified Water must meet the requirements for ionic and organic chemical purity and must be protected from microbial contamination. The source or feed water for the production of Purified Water is Drinking Water. It should also be protected from recontamination and microbial proliferation.

Production

Purified water is commonly produced by ion exchange, reverse osmosis (RO), ultrafiltration or electro deionization processes and distillation. Ambient temperature systems such as ion exchange, RO and ultrafiltration are especially susceptible to microbiological contamination. It is essential to consider the mechanisms for microbiological control and sanitization.

– Control of temperature in the system by heat exchanger or plant room cooling to reduce the risk of microbial growth (guidance value < 25 °C).

– Provision of ultraviolet disinfection.
– Selection of water-treatment components that can periodically be thermally sanitized.
– Application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid);
– thermal sanitization at > 65 °C.

C) Highly purified water

Highly purified water (HPW) should be prepared from drinking water as a minimum-quality feed-water. Highly purified water is a unique specification for water found only in the European Pharmacopoeia. This grade of water must meet the same quality standard as water for injections (WFI), including the limit for endotoxins, but the water-treatment process used may be different. Current production methods include, for example, double-pass RO coupled with other suitable techniques such as ultrafiltration and deionization. HPW may be prepared by a combination of different methods such as RO, ultra filtration and deionization.

Production

Highly purified water (HPW) can be produced by double pass reverse osmosis coupled with ultrafiltration or by any other appropriate qualified purification technique or sequence of techniques. It is essential to consider the mechanisms for microbiological control and sanitization.
– Control of temperature in the system by heat exchanger or plant room cooling to reduce the risk of microbial growth (guidance value < 25°C).
– Provision of ultraviolet disinfection.
– Selection of water-treatment components that can periodically be thermally sanitized.
– Application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid);
– thermal sanitization at > 65°C.

D) Microbiological test for water

The microbiological and chemical testing for Water used in pharmaceutical plant, Conductivity testing establishes a sample's ability to conduct electricity, which relates to the number of dissolved salts (ions) in the sample, high ion count lowers water purity and may indicate a processing problem.

Procedure

Transfer aseptically 1ml of the sample in each of two sterile petri dishes. Add to each dish approx. 20ml of sterile nutrient agar/ soyabean casein digest ager cover the petridishes and mix the sample with the agar by rotating the dishes 3 times both in clockwise and anti-clockwise directions. Allow the agar to solidify at room temperature. Invert the petridishes and incubate them at 37°C for 48 hrs. After incubation, examine the plates for growth and count the number of colony forming units in each plate. The average of both the readings is the total microbial count per ml.

E) Water for Injection

Water for injection (WFI) is used as an excipient in the production of parenteral and other preparations where product endotoxin content must be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral product-contact components. Water for injections should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feed water.

Production

Control of the chemical purity of WFI presents few major problems. The critical issue is ensuring consistent microbiological quality with respect to removal of bacteria & bacterial endotoxin. Distillation has a long history of reliable performance & can be validated as a unit operation, hence it currently remains the only official method for WFI. WFI in bulk is obtained from water or from purified water by distillation in an apparatus of which the parts in contact with water are of neutral glass, quarts or suitable metal & which is fitted with an effective device to prevent the entrainment of droplets. The correct maintenance of the apparatus is essential during production & storage, appropriate measures are taken to ensure that the total viable aerobic count is adequately controlled & monitored. WFI complies with test for purified water with additional requirements for bacterial endotoxins (not more than 0.25 IU of endotoxin per ml), conductivity & total organic carbon. Control of temperature in the system by heat exchanger or plant room cooling to reduce the risk of microbial growth (guidance value < 25°C). Provision of ultraviolet disinfection. Selection of water-treatment components that can periodically be thermally sanitized. Application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid); – thermal sanitization at > 65°C.

Uses of water in pharmaceutical and biotechnology[16]

- Parenteral,
- Ophthalmic,
- Cytotoxic preparation,
- Haem of iltration haemodia filtration solution,
- Peritoneal dialysis solution,
- Irrigation solution,
- Nasal/ear preparation,
- Cutaneous preparation,
- Buffer preparation,
- Oral preparation
- Clean in place process

Quality of water for pharmaceutical use[1]

Validation and qualification of water purification, storage and distribution system are a fundamental part of GMP and form an integral part of the GMP inspection. The grade of water used at different stages in the manufacture of the active pharmaceutical ingredients and pharmaceutical products should be discussed. The grade of water used should take account of the nature and intended uses of the finished product and the stage at which the water is used. The following tables provide some general examples for guidance.

Table 1: Quality of water for sterile medicinal products[1]

Minimum acceptable quality of water	Sterile medicinal products
WFI	parenteral
Highly Purified water	ophthalmic
WFI WFI WFI WFI	Hemofiltration solutions Haemodia filtration solution Peritoneal dialysis solution Irrigation solution
Highly Purified water Highly Purified water	Nasal/ear preparations Cutaneous preparations

System reviews[2]

1. Reliability;
2. Quality trends;
3. Failure events;
4. Investigations;
5. Out-of-speci"cations results from monitoring;
6. Changes to the installation;
7. Updated installation documentation;
8. Log books;
9. The status of the current SOP list. For new systems, or systems that display instability or unreliability, the following should also be reviewed:
10. Need for investigation;
11. Corrective actions and preventative actions (CAPA);

Inspection of water systems[2]

A tour of the water generation plant and visible pipework (including user points) should be performed to ensure that the system is appropriately designed, installed and maintained (e.g. that there are no leaks and that the system matches the piping and instrumentation diagram or drawing (P&ID). following list identi"es items and a logical sequence for a WPU system inspection or audit:

- a current drawing of the water system showing all equipment in the system from the inlet to the points of use along with sampling points and their designations;
- approved piping drawings (e.g. orthographic and/or isometric);
- a sampling and monitoring plan with a drawing of all sample points; – training programme for sample collection and testing;
- the setting of monitoring alert and action levels;
- monitoring results and evaluation of trends;
- inspection of the last annual system review;
- review of any changes made to the system since the last audit and a check that the change control has been implemented;
- review of deviations recorded and their investigation;
- general inspection of system for status and condition;
- review of maintenance, failure and repair logs;
- checking calibration and standardization of critical instruments.

Decontamination Techniques[3]

After an intentional contamination attack on a water system, there is a concern that some of the contaminant could remain on the interiors of the storage tanks, distribution system pipes, or in home fixtures. Decontamination of that infrastructure may be necessary to remove the contaminants from the interiors so that the residual contaminant does not pose a health or aesthetics problem. The disinfection chemicals described in the water treatment section may also play a major role in decontaminating a water system. High levels of disinfectant put into a storage tank (or pipe network) will inactivate many of the organisms that attached themselves to the interior structures. The high levels of disinfectants could also disrupt the normal biofilmin the system that some of the contaminants could hide in and not come out during routine flushing. In many cases, the flushing technique described above will be done at the same time that high levels of disinfectant are added to the flush water.

Water activity in ICH[21]

Water activity is the best index for microbial growth. A product may contain a relatively large percentageof moisture, but if the water is chemically “bound” to humectants or solutes, such as salts, sugars, or polyols, the water is biologically unavailable formicrobial growth. The water activity concept hasserved microbiologists and food technologists fordecades and is the most commonly used criterionfor food safety and quality.

Water Activity in QbD[21]

A drug manufacturer that decides to develop theirnonsterile drug release program based on Qb Dprinciples needs to identify their CQA’s. If theydetermine that microbial attributes are one oftheir CQA’s, they will need to setup one or several CPP’s that will describe the microbial safety of their product.

Water Quality Specifications for Pharmaceutical Water[1]

The USP and EP have adopted similar standards for the quality of Bulk Pharmaceutical Waters, as illustrated in Table. In addition to PW and WFI, the table also shows a grade called Highly Purified Water (HPW), as defined in EP and representing water meeting WFI specifications

COMMEON METHODS OF WATER PURIFICATION[6,7,8,9,10,11,12,13,14]

A) Boiling

This is undoubtedly the best method, but it is often inconvenient and wasteful of fuel supplies or natural resources. Water should be kept continuously boiling for minutes, which is sufficient at any altitude. The water must be covered when cooling to prevent recontamination, and it will also taste better.

B) Filters and pumps

There are now many devices available for purifying water but care must be taken in choosing the right one for your expedition. Some devices employ a simple filtration method, whereby water is pumped through tiny holes through which organisms are unable to pass. Be careful to look at the pore size (measured in microns), as anything greater than micron will not remove all organisms. Other devices employ both a filter and chemical treatment which strains and sterilises in one go. Choosing the right device is important, so here are some tips:

- Manufacturers often say how many litres of pure water a device will produce. However, this can be drastically reduced if the water is silty.
- If heavy use is expected, make sure that the purifier can be taken apart, cleaned and reassembled in the field to prevent blockages.
- Check the pump rate as some can take a lot of effort to produce a small amount of water.
- Many manufacturers of pumps go to great lengths to state what they will remove, while keeping quiet about what is not removed. For example, pumps will not remove chemical effluent, such as mercury in the tributaries of the Amazon, without the addition of a carbon filter. For those visiting areas where there is mining or factories up-river this may be important.
- Water storage time is also important; ideally after sterilisation the water should be used within hours.

Water Purification Technique For Pharma Industry

A) Steam distillation

Steam distillation is a special type of distillation (a separation process) for temperature sensitive materials like natural aromatic compounds. It once was a popular laboratory method for purification of organic compounds, but has become obsolete by vacuum distillation. Steam distillation remains important in certain industrial sectors.

Many organic compounds tend to decompose at high sustained temperatures. Separation by distillation at the normal (1 atmosphere) boiling points is not an option, so water or steam is introduced into the distillation apparatus.

B) Fractional distillation

Fractional distillationis the separation of a mixture into its component parts, or fractions, separating chemical compoundsby their boiling point by heating them to a temperature at which one or more fractions of the compound will vaporize. It uses distillation to fractionate. Generally the component parts have boiling points that differ by less than 25 °C from each other under a pressure of one atmosphere. If the difference in boiling points is greater than 25 °C, a simple distillation is typically used.

C) pot still

A pot still is a type of distillation apparatus or still used to distill alcoholic spirits such as whisky or cognac. Pot stills operate on a batch distillationbasis (as opposed to a Coffey or column stills which operate on acontinuous basis). Traditionally constructed from copper, pot stills are made in a range of shapes and sizes depending on the quantity and style of spirit desired.

D) Vacuum distillation

Vacuum distillation is a method of distillation whereby the pressure above the liquid mixture to be distilled is reduced to less than its vapor pressure (usually less than atmospheric pressure) causing evaporation of the most volatile liquid. (those with the lowest boiling points). This distillation method works on the principle that boiling occurs when the vapor pressure of a liquid exceeds the ambient pressure. Vacuum distillation is used with or without heating the mixture.

E) Distillation

Distillation is a process of separating the component or substances from a liquid mixture by selective evaporation and condensation. Distillation may result in essentially complete separation (nearly pure components), or it may be a partial separation that increases the concentration of selected components of the mixture. Commercially, distillation has many applications. For example:

- In the fossil fuel industry distillation is a major class of operation in obtaining materials from crude oil for fuels and for chemical feed stocks.
- Distillation permits separation of air into its components
- notably oxygen, nitrogen, and argon for industrial use.
- In the field of industrial chemistry, large ranges of crude liquid products of chemical synthesis are distilled to separate them, either from other products, or from impurities, or from unreacted starting materials.
- Distillation of fermented products produces distilled beverages with a high alcohol content, or separates out other fermentation products of commercial value.

An installation for distillation, especially of alcohol, is a distillery. The distillation equipment is a still.

Distillation is a very old method of artificial desalination.

F) Reverse Osmosis

Reverse osmosis (RO) units employ semipermeable membranes. The “pores” of RO membranes are actually intersegmental spaces among the polymer molecules. They are big enough for permeation of water molecules, but too small to permit passage of hydrated chemical ions. However, many factors including pH, temperature, and differential pressure across the membrane affect the selectivity of this permeation. Other concerns associated with the design and operation of RO units include membrane materials that are extremely sensitive to sanitizing agents and to particulate, chemical, and microbial membrane fouling; membrane and seal integrity; the passage of dissolved gases, such as carbon dioxide and ammonia; and the volume of wastewater, particularly where water discharge is tightly regulated by local authorities. Failure of membrane or seal integrity will result in product water contamination. Methods of control involve suitable pretreatment of the influent water stream, appropriate membrane material selection, integrity challenges, membrane design and heat tolerance, periodic sanitization, and monitoring of differential pressures, conductivity, microbial levels, and TOC.

G) Deionized Water

This water is produced by an ion-exchange process in which the contaminating ions are replaced with either H+ or OH– ions. Similarly to Distilled Water, Deionized Water is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for transferring an analyte within a test procedure, as a calibration standard or analytical blank, and for test apparatus cleaning.

H) Ammonia-Free Water

Functionally, this water must have a negligible ammonia concentration to avoid interference in tests sensitive to ammonia. It has been equated with High Purity Water that has a significantly tighter Stage 1 conductivity specification than Purified Water because of the latter's allowance for a minimal level of ammonium among other ions. However, if the user's Purified Water were filtered and met or exceeded the conductivity specifications of High Purity Water, it would contain negligible ammonia or other ions and could be used in lieu of High Purity Water.

I) Lead-Free Water

This water is used as a transferring diluent for an analyte in a Lead 251 test. Though no specific instructions are given for its preparation, it must not contain any detectable lead. Purified Water should be a suitable substitute for this water.

J) Activated Carbon

Granular activated carbon beds adsorb low molecular weight organic material and oxidizing additives, such as chlorine and chloramine compounds, removing them from the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. Control measures may involve monitoring water flow rates and differential pressures, sanitizing with hot water or steam, backwashing, testing for adsorption capacity, and frequent replacement of the carbon bed Activated carbon is used inpretreatment to remove chlorine andchloramine from feedwater so theydo not damage membrane filters and ion exchange resins.Most activated carbon is producedby “activating” charcoal fromcoconut shells or coal by roastingat 800 – 1000°C in the presence ofwater vapour and CO2.

CONCLUSION

1) Tight water management is a serious and critical point for pharmaceutical manufacturers—throughout the entire water operations.

2) Unique designs and proven, innovative integrated operations can provide creative solutions that result in significant operational cost savings, greater regulatory compliance and ultimately reduced business risk.

3) In addition, companies can implement “green” solutions, which support public and shareholder expectations with the benefit of greater marketplace competitiveness.
a) Steam distillat
b) Fractional distillation
c) Pot still
d)Vacuum distillation
e) Theoretical plate

4) The proposed design is easy, economical to maintain, and ecological because it has no high-efficiencyfilters, eliminating the constant regeneration ofthe ionic exchange resins.

5) It should also be pointedout that stainless steel tanks for decalc ified and purifiedwater can be sterilized easi ly and regularly bymeans of clean steam.

6) Therefore, validation of the system will ensurethe production of water will bedependable and withinthe specified limi ts.

7) In this case it will be easy 10prove that the price of the purified water will becompetitive and, in practice, less expensive thenother water-producing systems.

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