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A Review article on Purified water testing in pharmaceutical industry

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ABSTRACT :

Water is really important in making medicines. It affects how good the products are, how well they work, and how safe they are for patients. That's why it has to meet high-quality standards. To make sure the water is safe to use, there's a process called water qualification. This involves checking the water against regulatory rules, which includes testing it for physical, chemical, and microbiological properties. The article talks about the different types of water used in the pharmaceutical industry and highlights the need for validation and ongoing checks to keep the water clean and safe. It also mentions the importance of having a solid water management system that ensures regular maintenance and control measures to keep water quality up during the manufacturing process. In summary, the article emphasizes how necessary water qualification is for protecting the quality of medicines and ensuring patient safety.

Introduction:-

Water is essential for life and plays a key role in the pharmaceutical industry, impacting drug creation, cleaning equipment, and conducting tests. However, human activities are increasingly polluting water sources, leading to health hazards. In the pharmaceutical sector, water needs to meet very high purity standards to prevent contamination from things like organic carbon, salts, and microbes. Organizations like the USP, BP, EP, and JP set strict guidelines for pharmaceutical water quality, categorizing it into various grades such as Purified Water and Water for Injections (WFI). The European Pharmacopoeia has adapted to permit methods like reverse osmosis for producing WFI, making its standards more in line with those of USP and JP. They've also updated rules around testing for bacterial endotoxins, taking a more general approach to assess the risk of fever-causing substances in drugs. While tap water is safe to drink, that doesn't mean it's fit for pharmaceutical or industrial use. Therefore, pharmaceutical companies need to have specific systems for purifying, storing, and distributing water to ensure it meets strict quality guidelines. Purified water is vital for many uses, including preparing medications, treating patients in hospitals, and formulating nutritional solutions for those in need.[1]

Purified Water System:-

In the pharmaceutical field, purified water is created from drinking water using purification systems that have been thoroughly checked to meet high- quality standards. These include criteria for ionic purity, low total organic compounds, and minimal microbial presence. Brazilian health laws and global pharmacopeias set these guidelines, highlighting the importance of keeping microbial contamination in check, especially biofilms that might affect water quality. To ensure safety, regular cleaning and monitoring for microbes are necessary. There are specific levels for alerts and actions, depending on how the testing is done. Contamination from gram-negative bacteria such as Pseudomonas is a major concern because these bacteria can form biofilms and produce harmful endotoxins. While some regulations may not specify limits for these bacteria, it is still important to keep an eye on their presence. [2]Water plays a vital role in making pharmaceuticals, used in processing, as an ingredient, and for cleaning purposes. Regulatory advice from organizations like the FDA, WHO, and pharmacopeias—such as USP, EP, and JP—provides guidance on how to ensure water meets both chemical and microbial standards. USP documents set out minimum chemical criteria for various types of bulk water, including Purified Water and Water for Injection, while microbial standards can differ based on the intended use. Since results from microbial tests can take time, it is important to use real-time monitoring and validation systems to maintain quality. In conclusion, pharmaceutical water systems need careful design, validation, and ongoing maintenance to guarantee the consistent production of high-quality water, protecting both product quality and patient health.[3]

SOURCE OR FEED WATER CONSIDERATIONS:-

For pharmaceutical water to be of good quality, the initial source must meet the standards set by the U.S. EPA's National Primary Drinking Water Regulations or similar guidelines from places like the EU, Japan, or WHO. These rules help keep harmful pollutants in check, making it easier for purification processes to do their job. Sometimes, this means certain tests for substances like heavy metals or trihalomethanes (THMs) can be skipped altogether after further purification.[4]

It's also really important to keep the water safe from microbes. That means the water has to be free of coliforms, especially those that come from feces, to avoid any harmful bacteria. To fight off these microbes, municipal water systems often use disinfectants like chlorine. However, this can lead to the creation of unwanted by-products like THMs and haloacetic acids (HAAs) when chlorine reacts with natural organic matter. These by- products can pose health risks and come with their own set of regulations. There are other disinfectants like ozone, chloramines, and chlorine dioxide that can help lower the levels of these by-products, but they bring their own difficulties. Some of these chemicals might harm purification systems and leave behind compounds like ammonia, which can mess with purification and make the water fail quality checks, such as conductivity tests. That's why it's so important to create pretreatment systems that can effectively get rid of both the disinfectants and their by-products. For this to work well, pharmaceutical companies and municipal water suppliers need to work closely together to handle any changes in disinfection methods and ensure that the water quality stays consistent.[5]

Types of Water:-

The USP identifies different kinds of water used in the pharmaceutical field, mainly divided into bulk and packaged categories. Bulk water is usually made and used at the facility itself, whereas packaged water is created, sterilized, and sealed to keep it pure for as long as it is stored. There are also some types of water that aren't officially listed but are used for testing purposes, and it falls on the users to make sure these waters are appropriate for their needs.[6]

Purified Water This type of water is essential for producing and testing drugs that are not given directly into the body. It is created from drinking water through methods such as reverse osmosis or distillation. While it is cleaned well both in terms of chemicals and germs, it is not sterile. This means that if it is not stored correctly or used soon after being prepared, it can easily become contaminated with microbes.

Water for Injection (WFI) Water for Injection (WFI) has a chemical purity that's like Purified Water, but it has to meet extra standards for very low endotoxin levels, which makes it safe for use in injections. This water is created using distillation or other approved methods and needs to be sterile when packed in large quantities.[7]

Water for Hemodialysis Water used for Hemodialysis needs to be very clean and must have low levels of chemicals and germs. Even though this water is not meant for injections, it still has to meet strict standards for things like conductivity, organic materials, microbes, and endotoxins because it comes into direct contact with the blood during the dialysis process.

Pure Steam Pure Steam is made from pretreated water and is used for sterilization and cleaning. It's really important that this steam is completely free of impurities and any gases that don't condense since its condensate comes into contact with products or their containers. For it to work well, proper condensation is essential. Although not all features have specific definitions, they are important for certain uses. Different types of packaged waters are available, such as Sterile Purified Water, Sterile Water for Injection, Bacteriostatic Water for Injection, Sterile Water for Irrigation, and Sterile Water for Inhalation. These sterile waters are meant for situations where sterility is necessary or if a purified water system isn't available. Each type has particular uses and requirements for how it's stored, and while they are sterile, the packaging can sometimes leach impurities over time. Sterile Water for Injection and its bacteriostatic counterpart are used for injectable products, and they come with strict guidelines about container size and microbial content. Sterile Water for Irrigation is tailored for procedures that need a lot of water, while Sterile Water for Inhalation is designed for respiratory treatments but is not safe for injection because it has higher endotoxin limits. When it comes to manufacturing, Drinking Water, or Potable Water, is the basic quality standard and is necessary for initial cleaning, ingredient mixing, and as a source for higher purity pharmaceutical waters. It has to follow regulations from agencies like the EPA, EU, Japan, or WHO. While its quality can change with the seasons, systems that utilize it need to be built to handle this variability. Hot Purified Water is also mentioned; it's generally used to help dissolve ingredients during preparation, though there's no specific temperature required. In laboratories, various types of water are used, often labeled by their preparation methods or intended uses. Distilled Water and Deionized Water are popular choices for preparing reagents and cleaning, but in many cases, you could use Purified Water instead. Freshly Distilled and Freshly Deionized Water are meant for immediate use to avoid contamination, especially for things like animal injections or sensitive chemical tests. Deionized Distilled Water is a highly purified option saved for critical tasks like chromatography where very low impurities are necessary. There are also other types like Filtered Distilled Water or Deionized Water and simply Filtered Water, which have gone through fine filters to remove particulate matter, especially for injection tests. High Purity Water, detailed in USP <661>, is even more purified, showing very low conductivity and needing careful handling to keep it pure. It's the best choice for tests that demand the cleanest water possible. Some waters are categorized by their chemical makeup. Ammonia-Free Water must not contain ammonia to prevent interference in analyses, while Carbon Dioxide-Free Water is made by boiling and cooling to get rid of CO_2, often used in tests sensitive to pH or optics. Boiling helps get rid of gases, but deionization can do the same thing if you control exposure to the atmosphere afterward.[8-10]

Deaerated Water Deaerated Water is really just Purified Water, but with much less air dissolved in it. You can make it by boiling, using sound waves, or filtering under a vacuum. This type of water is important in tests where bubbles might mess with the results, like in dissolution testing and chromatography. Recently Boiled Water is a bit different; it's used once it has cooled down and is great for tests that can be affected by oxygen, carbonates, or air bubbles, such as when measuring pH or specific gravity.

Oxygen-Free Water Oxygen-Free Water isn't clearly defined in standard guidelines, but it plays an important role in tests that involve substances sensitive to oxidation. This type of water is usually made by bubbling inert gases like nitrogen or helium through it and needs to be stored in a way that keeps oxygen from getting back in. On the other hand, LAL Reagent Water, which is also known as endotoxin-free water, must not have any detectable endotoxins because it's used in the Bacterial Endotoxins Test with the Limulus amebocyte lysate reagent. This water usually comes from Water for Injection and might be sterilized further, ensuring it doesn't interfere with test results.[11]

Organic-Free Water Organic-Free Water is especially important for tests like Organic Volatile Impurities (USP <467>) that rely on gas chromatography. To keep things accurate, this water needs to have very few organic pollutants to prevent any unwanted signals during testing. It is made using high-quality purification techniques and is kept in clean storage to ensure it doesn't get contaminated again.

Lead-Free Water Lead-Free Water is essential for tests like USP <251>, where lead cannot be detected at all. Although it doesn't follow a specific preparation process, Purified Water can be used if it's tested and confirmed to be lead-free through methods such as ICP- MS or AAS. On the other hand, Chloride-Free Water is used in tests that are sensitive to chloride ions and must not interfere with reagents that react to chloride. Here too, Purified Water might be acceptable, provided it is verified.[12]

Hot Water Hot water is mostly described by how warm it is instead of a specific makeup of chemicals. It serves many purposes, like dissolving substances and cleaning things up or getting volumes ready in various mixtures. The level of purity in hot water is usually about the same as that of purified water.

UNIT OPERATIONS CONCERNS:-

Every part of a water purification system is important to make sure the final water quality is up to par. The introduction highlights that how well the whole system works depends not just on how each piece performs, but also on how they work together. Therefore, it's important to pay close attention during the design, installation, operation, and upkeep of each part. The validation process is key here; it ensures that the system reliably produces high-quality water in different real-life situations through thorough documentation, monitoring, and checking. The first line of defense in this system is prefiltration, which eliminates larger particles, usually between 7 to 10 micrometers, from the source water. This step is sometimes called depth filtration or coarse filtration, and it uses media capable of holding a lot of dirt to trap things like silt, sand, and organic material. Prefiltration can involve larger granular bed filters for big systems or smaller cartridge filters for smaller setups. Even though this step occurs early in the process and often before disinfectants are taken out, there is still a risk of microbial growth due to possible biofilm formation. Some challenges here include media channeling, clogging, incorrect sizing, and media loss during backwashing. It's important to maintain proper flow rates, conduct timely maintenance, and design carefully to keep filtration effective and protect the parts that come after. Activated carbon beds, usually made from granular activated carbon (GAC), play an equally important role by trapping low molecular weight organic compounds and removing harmful agents like chlorine and chloramine. These substances can damage delicate equipment downstream, so it's vital to get rid of them. However, GAC beds come with their own set of challenges. They have a porous structure that can encourage microbial growth, especially once disinfectants are removed from the water. They are also susceptible to hydraulic channeling, which can limit the water's contact with carbon, leading to less effective treatment. Once they get exhausted, GAC beds cannot be regenerated in place and need to be replaced. During their use, they might release fine carbon particles or bacteria, which could contaminate the system unless there are additional filtration measures. Keeping microbial growth under control in carbon beds is a tough task. Steam sanitization often fails because of steam channeling, making hot water a more dependable option for cleaning. In addition, microbial biofilms can cause carbon particles to stick together, making backwashing difficult and cleaning less effective. This situation can lead to more contamination and worsen performance. Alternative solutions like disinfectant-neutralizing chemicals or regenerable scavenging devices do exist, but they have their own limitations and aren't always a good substitute for GAC.[13-15]

CHEMICAL CONSIDERATIONS:-

The TOC test has taken the place of the older "oxidizable substances" test, which focused on organic impurities. Meanwhile, the conductivity test has largely replaced many inorganic tests, such as those for ammonia, chloride, and sulfate, though we still keep the heavy metals test. We decided not to include heavy metals testing because:

1. Stricter limits for heavy metals are already set for source water.
2. The modern materials used in water systems don't tend to leach heavy metals.
3. There hasn't been any proof of test failures just because of heavy metals in years of usage.

That said, it's still a good idea to keep records showing that heavy metals are absent during system checks or validation, considering the risks they can present. We also stopped using total solids and pH tests. Most things detected by total solids can be measured by TOC and conductivity, except for colloidal silica, which is generally harmless and is usually removed in treatment. We found pH to be unnecessary since it is already considered when measuring conductivity. The limits for conductivity were carefully worked out using the two least conductive ions, chloride and ammonia, adjusted for their pH ranges, along with natural ions from water and atmospheric CO_2. The process has three stages:

- Stage 1: Online testing with a specific temperature limit (for example, 1.3 µS/cm at 25°C).
- Stage 2: A fixed limit of 2.1 µS/cm as a cautious baseline.
- Stage 3: Lab testing compares the conductivity readings with pH to confirm they meet the standards.

This step-by-step method ensures that if the water passes the new conductivity checks, it would have also met the old chemical tests, making this change both scientifically sound and easy to implement.[16]

Conclusion

Getting to know the different types of water used in making medicines—like how they are prepared, what their standards are, and what they are used for—is really important for keeping quality in drug production. This article points out how vital it is to follow the rules set by authorities and to carry out quality checks to keep the right qualities of pharmaceutical water. As we see changes in water sources and treatment methods, sticking to strict water quality standards will remain a key part of making pharmaceuticals, which ultimately affects public health and safety.

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