Microbiological Study of a New Design of PW/WFI

Pretreatment and Production System

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The main challenge for the manufacture of Water for Injection (WFI) is meeting the maximum bacterial levels, since meeting the chemical criteria is usually easily attained. The microbiological criteria are very hard to meet as the regulatory maximum is less than 10 cfu/100 ml. Internal action levels and/or alert levels must always be below 10 cfu/100 ml, so keeping reliably within specifications is a very hard task.

In the case study, the Electrolytic Scale Reduction (ESR) and Hydro Optic Dechlorination (HOD) are pretreating water feeding a hot water sanitizable Reverse Osmosis (RO) and hot water sanitizable Continuous Electrodeionization (CEDI). This system, constantly produced WFI quality water over a period of 3 years. This performance is remarkable in achieving WFI standards, even though there was only a single membrane barrier. This is because of the low level of bacteria in the pretreatment feeding the RO even though there are very high levels in the feed water.

1. Introduction

Most modern and GMP Purified Water (PW) generation systems are based on Reverse Osmosis (RO) membranes. The system has to meet both chemical and microbiological criteria to achieve operational and regulatory goals.

The common chemical criteria to be met in the RO pretreatment are: hardness reduction and chlorine removal. The microbiological criteria are a not to be exceeded total count and absence of pathogens.

The design of the systems, both pretreatment and production, must meet the chemical criteria while taking into account many common and well known design issues which depend on feed water parameters. The feed water parameters are easily ascertained by laboratory analysis. Well known and tested engineering rules are used to design equipment which can achieve the essential chemical criteria. Given accurate and extensive feed water data, very reliable chemical results can be expected.

Systems are designed to meet the bacterial criteria in spite of highly unstable parameters in the feed water. The final bacteriological performance of a system is an amalgam of: initial design, installation standards, day to day operation and regular maintenance. This also includes feed water bacteriological levels and microbial species, feed water TOC levels and water temperature as well as other parameters that are hard to define and measure. Because of the wide variety of impacting parameters, it is very hard to predict in advance the propensity of bacteria to grow on the organic media usually used in the pretreatment, e.g. softener resins and/or Active Carbon (AC). Apart from the possible growth in the softeners and AC, all incoming bacteria from the municipality are removed by the RO membrane and concentrated in the reject compartment. This high concentration is conducive to biofilm growth with the associated reduction in RO performance.

In order to forestall out of specification bacteriological results maintenance departments usually resort to an overkill approach and sanitize the equipment on a weekly basis, with very little option to change as they are severely limited in the ability to predict the microbial growth over different seasons with changing bacterial levels in the feed water.

A new system for pretreatment of RO feed water in pharma plants will be presented in this article. The system actively reduces incoming bacterial levels, freeing the RO from bacterial ingress, while effectively disinfecting the feed water on its passage through the pretreatment equipment into the membranes. This system operates without organic media and without resins. There is no need for chemical disinfection as the system is self-cleaning. This system operates while consistently reducing the bacterial levels and preventing microbial colonization of the equipment. The system operates with no moving parts and without need of rinses or backwashes.

2. Background

Water systems need to be operated and maintained in a controlled manner. In addition, the source water has to meet potable water standards as defined by the relevant organizations in the US, EU, Japan or by the WHO. As bacteria will proliferate if conditions are favorable, even low levels of feed water microorganisms can lead to out of control downstream results [1]. If water microbial parameters exceed the potable water limits, after entering the boundaries of the PW/WFI generation, the operator will be hard pressed to demonstrate control of microbial level in the system.

If the bacterial levels in the treatment stages are increasing as the water advances through the system, this demonstrates loss of control even if the product water is still within acceptable limits.

The US, Europe and WHO have standards of *"zero"* detectable *"objectionable microorganisms"* even though they are sometimes detected in the municipal water [2, 3]. Carbon beds are the most prone to develop high levels of microorganisms of all sorts. An FDA inspector observed that *"the carbon filter is probably the weakest element in any DI system from the standpoint of microbial attack"* [4]. Bacteria can form mats and clumps on resin beads. The softener resin is organic and in conjunction with slow flow and eddies, that are needed for proper ion exchange, proliferation of unwanted growth is almost inevitable. Control of this biofilm is possible but only by considerable investment in routine maintenance. The needed maintenance can range from backwash and regeneration to sanitizations and rebeddings.

Extensive guidance for microbial sampling can be found in the ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam and Process Gases [5]. Areas that are worthy of attention were singled out. These are: deionization steps, carbon filters, depth filters, RO, Ultrafiltration (UF) and the final deionization process. It was recommended to perform species identification of the resident microflora and build up a picture of the local microbial population [6].

The regulatory authorities expect the system owner to control all aspects of the sampling of the system. This includes both the chemical and microbial results [7]. In a media-based water system, the only way to achieve this control is constant diligence and fast reactions in stamping out microbial outbreaks. This is a high, manpower intensive and time consuming effort. Microbial control in media based systems is limited in efficacy and has the potential for long periods of system and plant downtime.

3. System Based on Electrolytic Scale Reduction, Hydro Optic Dechlorination, Hot Water Sanitizable RO-EDI

3.1 Electrolytic Scale Reduction and Hydro Optic Dechlorination RO Pretreatment

An Electrolytic Scale Reduction (ESR) is a unit that reduces scale so as to eliminate the potential of scale precipitation on downstream RO membranes. The removal of scale precipitation in the membranes will allow regular and continuous operation of the RO with normal recovery percentages.

The system core has arrays of Stainless Steel (SS) reactors equipped with central electrodes. When an electrical field is effected between the electrode and the cylindrical reactor a current flows through the water. Some of the water dissociates into OH^- and H^+ ions [8].

The OH^- concentration on the inside of the reactor cylinder has the effect of raising the pH and causing precipitation of hardness scale. Some of the scale adheres to the cylinder and some will drop to the bottom of the reactor.

The scale builds up in the reactor until removed manually or automatically.

In the same way that the OH^- concentration on the inside of the reactor cylinder has the effect of raising the pH, the H^+ concentration on the central anode will have the effect of lowering the pH. This effect will cause some of the naturally occurring chlorides in the feed water to be activated as free chlorine.

The following formula denotes this reaction:

$Cl^- + H^+ \rightarrow HCL$

$HCl + HCl \rightarrow Cl_2 + H_2$

This free chlorine by-product disinfects the ESR and destroys biofilm as long as the system is in operation.

3.2 Removal of Oxidants in RO Feed Water by Way of UV Irradiation – Hydrodynamic Optical Dechlorination

Hydrodynamic Optical Dechlorination (HOD)

It is commonly known that UV radiation can destroy free chlorine [9, 10]. This reaction is a fast and reliable process that removes the oxidizing form of chlorine and neutralizes the possible damage that could occur to downstream RO and Continuous Electrodeionization (CEDI) as the by-products of the reaction are not oxidizing [9].

The process for breakup of chlorine in the common hypochlorous acid form is given as follows:

$2HOCl \rightarrow 2HCl + O_2$

A typical disinfection UV will generate at the end of the lamp life a dosage level [11] of 30,000 $\mu J/cm^2$. The dosage levels needed for removal of chlorine depend on the free chlorine concentration. If the HOD is specified to remove up to 1 ppm of free chlorine, the dosage levels needed are in the range of 1,500,000–1,800,000 $\mu J/cm^2$ [12]. The very high level of UV radiation will effectively dechlorinate the water and, as a welcome by-product, will also disinfect with a large over kill of more than 50 times.

3.3 ESR-HOD-RO-EDI Integrated System

All the above components can be integrated to generate PW. The ESR will reduce the scale in the feed

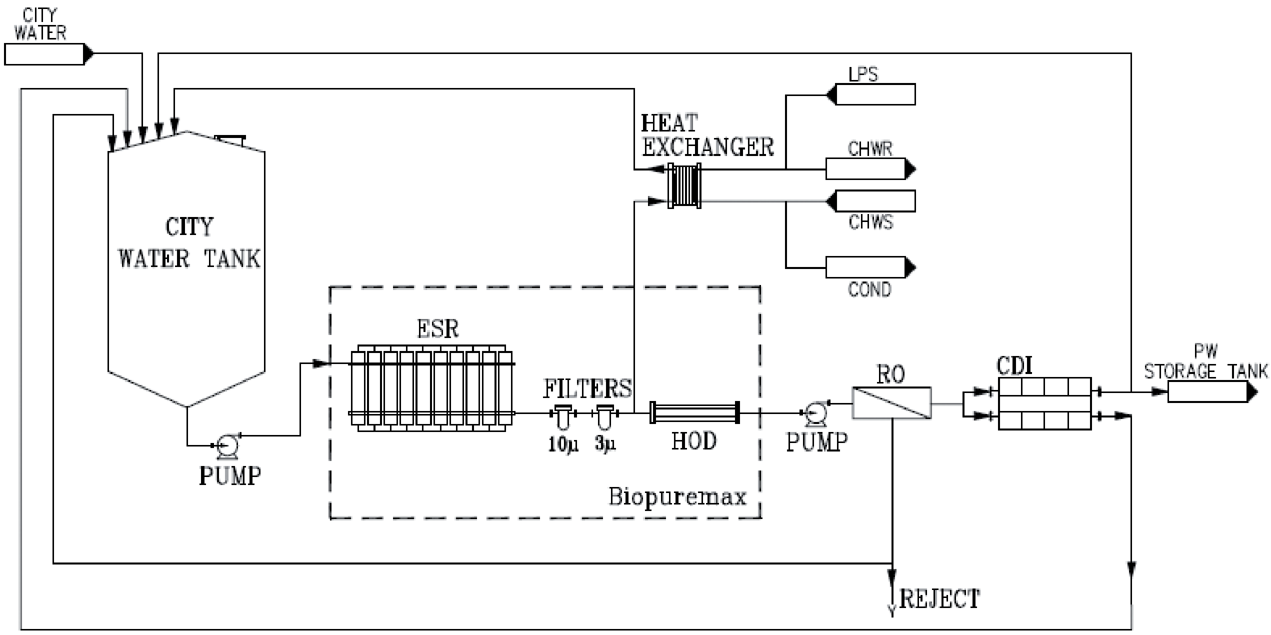

Figure 1: System Flow Diagram (Source: The figure was made by the author/Biopuremax Ltd).

water. It will also generate free chlorine as a by-product of the precipitation process in the reactors. This free chlorine is destroyed by the HOD that is installed in series to the ESR. The dechlorinated and scale reduced water can now be utilized as feed water for a conventional RO and EDI system (Fig. 1).

The RO and EDI will remove the ionic components and soluble organic compounds so as to meet PW monograph standards. Water for Injection can be generated by adding a second stage to the RO or by adding final Ultra Filtration (UF).

For startup or after maintenance, a sanitizing cycle is needed. As in traditional designs, chemicals can be used for sanitization, but a hot water sanitization can also be utilized as the ESR-HOD combination is fabricated of SS. There are many advantages of the hot water wash over the chemical sanitization. The hot water sanitization will penetrate biofilm with ease in comparison to chemical disinfectants [11], with the added advantage that with hot water there is no need to validate chemical removal before restarting the system. In addition, the hot water will be circulated from the municipal water feed all the way to the PW/WFI storage tank without leaving any areas that have not been heat sanitized.

■ 3.4 Continuous Bioburden Reduction (CBR)

As ion exchange, RO and UF are all particularly susceptible to microbial contamination, it is essential to consider mechanisms for microbiological control [13].

A well designed process should be capable of controlling bioburden and endotoxins from beginning to end. This is true of water systems as well as of any other production system.

The ESR and HOD technologies are no more susceptible to bioburden than SS pipes. All the surfaces are manufactured of SS or quartz and are easily hot-water sanitizable. As the ESR will also generate free chlorine, the system will actively reduce bioburden. The HOD destroys the free chlorine with high doses of UV irradiation which also disinfects the water. When the system is returned to operation after a filter or UV lamp replacement, a sanitizing cycle will remove contamination that might have been introduced by exposing the system to the outside environment.

■ Table 1

Site Data for Bioburden Criteria.

	Total Micro CFU/100 ml Average	*E. COLI* CFU/100 ml Average	*Pseudomonas* CFU/100 ml Average	Coliforms CFU/100 ml Average	Fungus CFU/100 ml Average
Product Water	0	0	0	0	0
WFI Criteria	< 10 CFU/ 100 ml	< 1 CFU/ 100 ml	< 1 CFU/ 100 ml	< 1 CFU/ 100 ml	< 1 CFU/ 100 ml
Number of Samples	141	141	141	141	141

Table 2

Site Data for Chemical Criteria.

	Endotoxin (EU/ml) Average	TOC (ppb) Average	Heavy Metals (ppm) Average	Nitrate < 0.1 mg/l Average
Product Water	< 0.005	< 50	< 0.1	< 0.1
WFI Criteria	< 0.25	< 500	< 0.1	< 0.2
Number of Samples	33	Online	33	32

4. Case Study

An ESR-HOD-Single pass RO-EDI has been operating for over 3 years. Table 1 summarizes the microbiological results within this time period. The results meet WFI criteria as they are below detectable limits.

Note: All microbial counts are averages and are all zero. Over the full sampling period, there was not one positive colony forming unit (CFU). The results are shown at a 100 ml resolution.

Table 2 summarizes the chemical characteristics of the water in the same 3 year period. The endotoxin average is below detectible limits, the online TOC was always below 50 ppb, heavy metals and nitrate were below the WFI criteria. In short, the system met WFI criteria for a period of 3 years without any Out of Specification (OOS) occurrences.

5. Conclusion

Pretreatment systems for RO have remained almost unchanged for the last 3 decades. The industry demands a new system, in which water is not wasted and no waste stream is generated as a by-product. The existing systems do not withstand high bioburden feed water and are liable to grow pathogens and to contaminate downstream filters and RO.

This new system stops proliferation of biofilm and pathogens and meets the pharmaceutical market demands of a well-designed pretreatment capable of controlling bioburden from beginning to end. The ESR-HOD pretreatment for pharmaceutical water is simple while providing effective results.

This system operates without chemicals, media, or resins, and eliminates the need for: regeneration, complicated instrumentation and feedback loops. The system operates without moving parts and without need of rinses or back washes. The CBR, demonstrated in the case study, is exactly what is needed to supply long term low levels of bacteria in the system. Standard SS fabrication materials facilitate hot water sanitization and serve to “reset” the bacteriological levels on a regular basis.

In the case study, the combination constantly produced WFI quality water, even though there was only a single membrane barrier. This is because of the low level of bacteria in the pretreatment feeding the RO.

LITERATURE

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