RO Water Pretreatment for Pharma Systems

Green Technology

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The traditional pretreatment for Reverse Osmosis (RO) feed water is softening in collaboration with Active Carbon Filtration (ACF). However, this combination is not optimal if the site has problematic mineral species or periodic high microbiological levels. The pretreatment with an Electrolytic Scale Reducer (ESR) and Hydro Optic De-Chlorination (HOD) has no need for regeneration, no organic media and no chemicals. This new system operates reliably and robustly, with low maintenance, without waste water and with low life cycle costs. This article covers the historical references, the status quo of Water for Injection (WFI) production and the traditional designs. Moreover, the new technologies ESR and HOD are explained to the reader. In order to give an example of WFI production by non-distillation technologies, a case study is presented. Last but not least, the article answers concerns of the regulatory authorities as to possible microbiological contamination of membrane based WFI generation.

Introduction

Distillation has been the flag holder as a final process in Water for Injection (WFI) production for as long as can be remembered, even though the United States Pharmacopeia (USP) has allowed production processes other than distillation. However, distillation has remained the "Gold Standard" [1].

This is not surprising, since the European Pharmacopeia (EP) has consistently held that WFI must not only meet the specifications of the monograph but must also be evaporated and condensed in a suitable distillation unit [2]. However, distillation has always been required as few companies produce exclusively for the American market.

On the other hand, there has been much interest in changing the EP's unequivocal demand for distillation. Surveys have shown that over 73 % of pharma users and over 77 % of system suppliers answered positively to the question: "*Is the manufacture of WFI through reverse osmosis (instead of distillation) interesting for you – respectively would it be an alternative for you if it were approved in Europe?*" [3]

This interest is understandable in the light of considerable savings of capital investment in equipment for membrane based systems vis–à–vis thermal production equipment. Indeed, membrane based pretreatment for distillation is recommended [4, 5] Thus, most WFI stills are fed with water meeting Purified Water (PW) standards. In this case, the investment in distillation units is in addition to the investment in membrane based production equipment.

As for operating costs: If the energy expenditure on evaporation and condensation of the feed water is saved by not installing distillation equipment, the total life cycle costs – investment and operational – can be drastically reduced.

It has taken many years for the EP to allow the use of membrane based technology, without need for final distillation. The process started in 1999 [6] when an international conference deliberated on whether to allow reverse osmosis (RO) with/without additional technologies, e. g. continuous electrodeionization (CEDI) and/or ultrafiltration (UF), as an alternative method for producing WFI without needing a still.

The main concern of the regulators was the possible microbiological contamination of WFI by not undergoing a thermal process of boiling, evaporation and condensation [6, 7].

In the European Compliance Academy (ECA) survey from 2011 [8], end users and system suppliers were asked why distillation was often used for WFI production in the US even though it was possible to use membrane based systems. Over 28 % of the end users and over 36 % of the system suppliers thought that with the present day systems the microbial risk was too high. In typical pretreatment systems, the chief operating concerns regarding active carbon are microbial build up and microorganism proliferation in softeners [9, 10]. These microbes will be fed directly to the RO membranes and cause surface contamination and fouling of those membranes with an impact on product water and operational parameters.

The EP is changing, but should the systems also be changed in view of

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these problems? A solution for these problems is the following technology, which will allow the production of WFI without distillation – based only on membranes.

New Media Free and Chemical Free Technology

Electrolytic Scale Reducer (ESR)

The ESR is an electrically powered reactor used to reduce scale in the RO feed water in order to inhibit scale precipitation on membranes.

The system has no moving parts and no organic resin softeners. There is no backwash, no regeneration and no chemical dosing. The ESR is based on electrical scale precipitation. The unit is composed of a metallic cylindrical reaction chamber, which is the cathode, with a central titanium electrode which is the anode.

An electrical current is passed through the water and some of the molecules are split into OH^- and H^+ ions. This split causes a very high pH to form on the inside of the cathode. As high pH is a critical factor in hardness precipitation per the Langelier Saturation Index [11], scale forms on the cathode and is removed from the water.

Since some of the scale has been removed from recirculating water, no hardness will precipitate on the RO membranes.

The following equilibrium denotes the chemical reaction [12]:

$Ca^{2+} + 2HCO_3^- \leftrightharpoons CaCO_3 + CO_2 + H_2O$

$Ca^{+2} + CO_3^{-2} \leftrightarrow CaCO_3$

The process will also reduce high levels of silica, ferrite and manganese contaminants. This is a special advantage as the removal of these contaminants is poorly met with the typical softeners with or without the addition of antiscalant.

ESR scale is removed from the cathode by reversal of the electric current which will drop the scale into the water and will then be flushed to drain.

The ESR has no moving parts and no consumables to be replaced.

An additional advantage of the ESR is the generation of free chlorine from the chlorides in the feed water inlet.

The following equilibrium denotes this reaction [12]:

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

$Cl + HCl \rightarrow Cl_2 + H_2$

This free chlorine by-product is a natural occurring factor keeping the ESR clean of biofilm.

Hydro Optic De-Chlorination (HOD)

The ESR treated water is de-chlorinated with a HOD unit, by exposure to UV irradiation which decomposes the free chlorine [13].

It is common knowledge that UV irradiation will reduce the concentration of free chlorine and chloramines [13, 14]. UV breaks the chemical bonds of free chlorine or chloramine to form hydrochloric acid and other byproducts. When irradiated with a sufficient dose of UV, the reaction for free chlorine, as hypochlorous acid, is as follows:

$2HOCl \rightarrow 2HCl + O2$

When irradiated with a sufficient dose of UV, the reaction for water containing chloramine and free chlorine, as hypochlorous acid, is as follows:

$2NH2Cl + HOCl \rightarrow N2 + 3HCl + H2O$

The RO membrane easily rejects the by-products of the reactions [13].

The HOD is a very powerful UV unit with medium pressure UV lamps which have high energy spikes at the needed wavelengths for chlorine destruction which are concentrated in the 240 nm and the 290 nm area [15].

In effect, the HOD has removed the oxidizing substances in the water, which could damage polyamide membranes and/or prevents damage to the downstream CEDI unit.

The HOD has no moving parts but needs a UV lamp replacement every 6 months.

As can be seen in Fig. 1, the photo-deactivation follows an exponential decomposition curve; the needed dose to reduce 1 ppm of free chlorine is above 1,700 mJ/cm^2.

Sometimes reduction from 1.5 ppm or from 2 ppm is needed depending on the type of pretreatment and the design safety factor in which case even higher dosages UV would be required.

Systems Configuration

Combining ESR, HOD, RO and CEDI

As can be seen in Fig. 2, the system starts with a city water tank, ESR and HOD units with intermediate filtra-

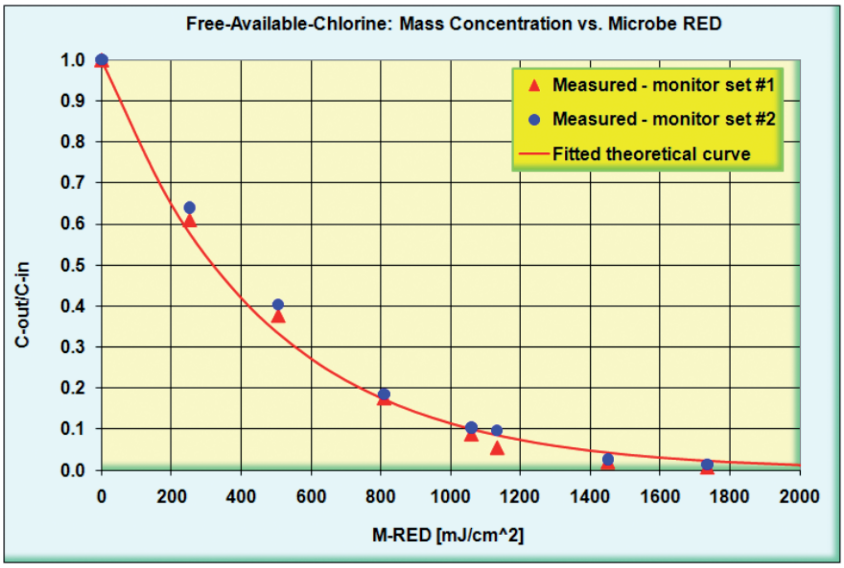

Figure 1: Exponential decomposition curve [16].

tion. This pretreated water is fed directly into a RO-CEDI combination.

The ESR and HOD are designed to undergo hot water sanitization at 85°–95 °C. The construction materials of the ESR are SS316L and titanium and those of the HOD are SS316 and quartz.

There is no bioburden as there is no organic media in the system. The system is hot water sanitized from city water inlet to the CEDI outlet and runs without complicated instrumentation or sophisticated feedback loops. Furthermore, it operates with no moving parts, other than pumps. Moreover, no rinses or back washes are needed.

The system has been operating for a total of 7 years in different sites. It complies to green policies as no water is wasted, no chemicals are used and no media is utilized or replaced.

Continuous Bioburden Reduction (CBR)

The destruction of bacteria is inherent in the continuous operation. As the system has no organic resin or carbon filter, there is no capture of microbes. When the system operates, it actively reduces the bioburden by the following process:

In the city water tank, the water volume is constantly being replaced and diluted with clean water from the ESR outlet (Fig. 2). The ESR constantly generates free chlorine. Keeping the ESR reactors free of growth by very high doses of UV irradiation, the HOD reduces the bioburden even further. The system requires hot water sanitization only on start up or after the UV lamp replacement.

Case Study

Combination of ESR, HOD, RO and CEDI for Water of WFI Quality

A number of industrial install sites were set up; one site is presented here where the total system perform-

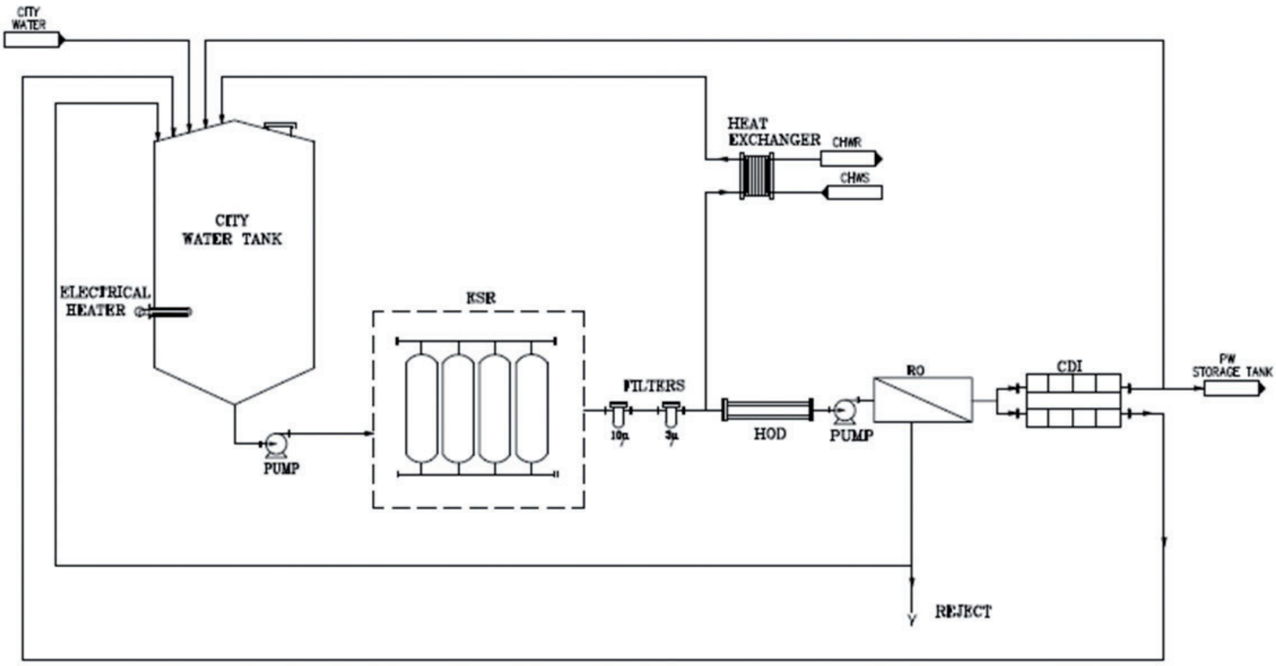

Figure 2: Flow diagram of ESR-HOD-RO-CEDI combination [12].

Table 1

PQ data, sampled over a 2 month period.

Position in system	Total Micro Count CFU/100 ml		E.COLI CFU/100 ml		Pseudomonas CFU/100 ml		Coliforms CFU/100 ml		Fungus CFU/100 ml	
	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
City water inlet	15,800	0–78,000	47	1–227	24	0–82	201	28–910	13	0–48
Exit City water storage tank	127	0–1,000	0	0	0.167	0–1	1.375	0–11	0	0
Exit ESR	50	0–300	0	0	0.167	0–1	0.25	0-4	0	0
Exit HOD	5	0–100	0	0	0.167	0–1	0	0	0.167	0–1

■ Table 2

PQ product data, sampled over a 3 years.

	Total Micro Count CFU/ml Average	E.COLI CFU/100 ml Average	Pseudomonas CFU/100 ml Average	Coliforms CFU/100 ml Average	Fungus CFU/100 ml Average	Endotoxin (EU/mL) Average	TOC (ppb) Average	Heavy Metals (ppm) Average	Nitrate < 0.1 mg/l Average
Product water	0	0	0	0	0	< 0.005	< 50	< 0.1	< 0.1
WFI Criteria	< 10 cfu/100 ml	< 1 cfu/100 ml	< 1 cfu/100 ml	< 1 cfu/100 ml	< 1 cfu/100 ml	< 0.25	< 500	< 0.1	< 0.2
Number of samples	141	141	141	141	141	33	Online	33	32

ance was studied for compatibility to WFI standards. The water production system combines the ESR, HOD, RO, CEDI technologies.

The pretreatment and production system was validated with the following condensed data shown in Table 1 [12].

As can be seen in Table 1, total average microbial counts are reduced by 4 logs. As EP microbial standards for WFI are < 10 cfu/100 ml [2], the RO feed water meets WFI microbial standards before passing through the RO membrane. The reduction of *Pseudomonas* is especially significant as this type of pathogen builds biofilm. Moreover, it is tenacious in its adherence to surfaces and typically resistant to most types of sanitization procedures.

Table 2 demonstrates that the product water has undetectable total count and no other microbial species. The values for Limulus Amoebocyte Lysate (LAL), Total Organic Carbon (TOC), heavy metals and Nitrate all meet the WFI water criteria.

Conclusion

A system utilizing an ESR and downstream HOD enjoys significant advantages when compared to traditional chemical and media based systems. No regeneration is required, nor any back washes. There are no added chemicals and no effluent.

As demonstrated in the case study, the system product water meets WFI standards even after 3 years of normal operation. No buildup of biofilm and microbial growth occurs during operation. When combined with full hot water sanitization, the system delivers true microbe-free pretreatment water.

This type of system answers all concerns of the regulatory authorities as to possible microbiological contamination. The robust system, if used to generate WFI, combines greatly reduced operational costs with high reliability. The ESR-HOD system saves precious water and retards bacterial growth while delivering highly reliable results over the full life cycle of the system.

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