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Cold Production of Water for Injection (WFI) Utilizing 3M™ Liqui-Cel™ Membrane Contactors for CO_2 Reduction

Background

In recent years, pharmaceutical manufactures have intensified their interest in exploring alternative technologies that are more economical and environmentally preferable. This has given rise to looking closely at membrane technologies in the production of Purified Water (PW) and Water For Injection (WFI).

Prior to April 2017, European regulations specified that WFI could only be produced by distillation. This changed when the European Pharmacopoeia (Eur. Ph.) monograph for WFI (0169) was revised allowing for the use of cold water by membrane technologies. This is in accordance to U.S. pharmacopoeia which already allowed the use of membrane technologies in cold water before 2017. The use of membrane technologies for PW and lately WFI production enables European pharmaceutical manufacturers to reduce energy consumption, chemical use and potentially initial investment costs. However, WFI water treatment systems utilizing membrane technologies have to be designed carefully to ensure water quality standards are met.

PW and WFI Quality Standards

The Eur. Ph. specifies limits of PW and WFI according to parameters like conductivity, dissolved organics (total organic carbon, TOC), nitrates, endotoxins and aerobic bacteria (colony forming units, CFU). Table 1 shows an overview of selected limits defined by the Eur. Ph. for PW and WFI. Conductivity limits depend on temperature and have to be considered in the process design.

Table 1: European Pharmacopoeia Limits Defined for PW and WFI

Parameter	PW	WFI
Conductivity [µS/cm]		
at 15°C	4.0	1.0
at 20°C	4.3	1.1
at 25°C	5.1	1.3
Total Organic Carbon [mg/l]	1.3	1.3
Colony Forming Units [CFU]	100 CFU/ml	10 CFU/ 100 ml
Endotoxins [I.U./ ml]	-	0.25
Nitrates [ppm]	0.2	0.2

To help meet conductivity limits 3M™ Liqui-Cel™ Membrane Contactors can be used to control the CO_2 content of pharmaceutical water instead of a caustic dosing upstream to reverse osmosis. As a membrane-based technology, Liqui-Cel Membrane Contactors fit well in systems that predominantly include membrane technologies to produce WFI from cold water.

3M Liqui-Cel Membrane Contactor Technology

3M Liqui-Cel Membrane Contactors contain hollow fiber membranes that allow a liquid and a gas to come into direct contact without mixing. Figure 1 shows a microporous hollow fiber membrane with water flowing on the shell side and vacuum and/ or sweep gas flowing on the lumen side.

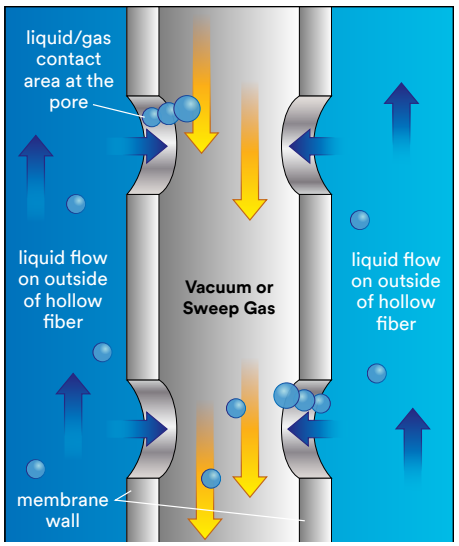


Figure 1: Hollow Fiber Membrane in a 3M Liqui-Cel Membrane Contactor

As the membrane is microporous and hydrophobic gases can pass through the membrane wall. Applying a vacuum and/ or sweep gas creates a partial pressure difference which is the driving force to remove the target gas. For CO_2 removal from water, air can be used as a sweep gas.

Example WFI System Design with EDI

Since tap water quality as feed may vary, water treatment systems show different designs. Here a typical set-up of the basic operation steps is explained for a membrane-based WFI system. Figure 2 shows a basic flow chart of a WFI generation system starting with tap water going to PW and ending up with WFI. The choice of technologies used in the first pretreatment step [A] depends on the source water quality and should ensure that subsequent membrane processes receive good quality feed water to reduce the risk of blocking or fouling the membrane. Pretreatment steps could include ultraviolet (UV) irradiation to inactivate microorganisms and filtration to remove particles.

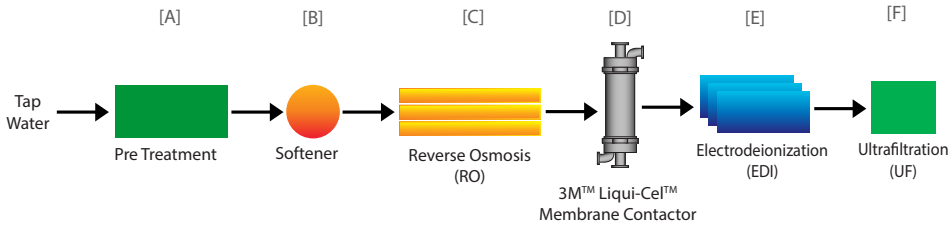
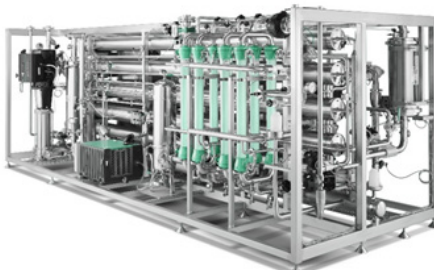


Figure 2: Process steps of WFI production including EDI

The Softening step [B] removes hardness minerals (e.g. Ca or Mg) to avoid precipitation that can cause scaling of Reserve Osmosis (RO) membranes. In step [C] RO membranes remove ions and reduce CFU and endotoxins, but dissolved free CO_2 is not rejected and passes into RO permeate and contributes to conductivity. Therefore, the permeate stream is fed into 3M™ Liqui-Cel™ Membrane Contactors [D] to reduce the CO_2 concentration to low levels. The subsequent Electrodeionization (EDI) step [E] polishes the water by further removing ions and ionizable gases, such as CO_2. Depending on the inlet conductivity, many EDI systems may not perform as efficiently with CO_2 levels above 5-10 ppm. This inlet limit and even lower concentrations down to 1 ppm CO_2 can be reached by membrane degassing.

After EDI Ultrafiltration (UF) [F] as final polishing a membrane filter is needed to further reduce CFU and endotoxins as a sterilization step to defined WFI quality limits. Picture 1-A and 1-B show front and back views of a WFI generation system following the design in Figure 2, courtesy of Syntegon Technology GmbH (Dresden, Germany) with UF modules as last filter step. The feed water has a conductivity of 502 µSi/cm. All membrane components have stainless steel (SS) housings (except UF) allowing for hot water sanitization. The 3M Liqui-Cel EXF-10x28 Series Membrane Contactor with SS housing is shown in the upper right corner of Picture 1-A. In this example, the degassing step removes CO_2 from maximum 177 ppm to <10 ppm. The complete system produces a WFI flow of 16.3 m3/h in the required quality according to Table 1.



Picture 1-A: Membrane based WFI production system. Courtesy of Syntegon Technology GmbH, Ger

Picture 1-B: Membrane based WFI production system. Courtesy of Syntegon Technology GmbH, Ger

Example WFI System Design without EDI

As mentioned water treatment systems can vary in design. Another possible set-up is the use of a double-permeate-stage RO with 3M Liqui-Cel Membrane Contactors in between the first stage and second stage RO as shown in figure 3. This design is without an EDI step downstream. However, the maximum CO_2 concentration after the membrane contactor has to be much lower than for previous design example with a target of <10 ppm CO_2 outlet concentration. As no EDI is present for polishing, the membrane degassing step has to be designed for a maximum CO_2 outlet of ≤1 ppm to meet the conductivity limits stated by Eur. Ph. A final membrane polishing filter is optional.

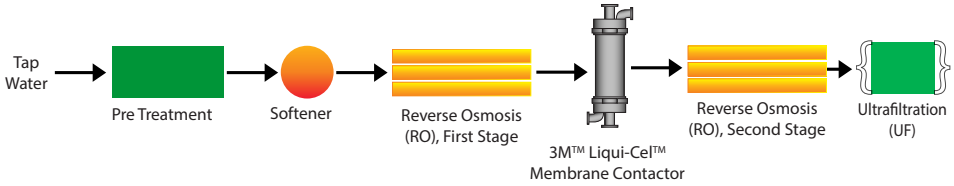


Figure 3: Process Steps of WFI production without EDI; Double-stage RO

Summary

Since 2017 it is allowed to produce WFI without distillation out of cold water with membrane-based technologies. Different designs can be used for WFI generation, but each interdependent production step has to be designed carefully in order to meet the defined limits by Eur. Ph. 3M Liqui-Cel Membrane Contactors are essential to help achieve Eur. Ph. conductivity limits for WFI production in both described designs without using chemicals.

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