REVERSE OSMOSIS

PRETREATMENT AND CLEANING OF RO SYSTEMS WITH CARBON DIOXIDE FOR THE PHARMACEUTICAL AND THE FOOD INDUSTRY

Pressurized carbon dioxide (CO_2) is a new and reliable treatment for aseptic purified water systems in accordance with United States Pharmacopeia (USP) and EG-GMP.

Men have used the preserving effect of CO_2 since ancient times (e.g., gas storage of corn under a CO_2 atmosphere). This effect is based on two primary factors: first, for its displacement of oxygen, and secondly, because the CO_2 has a direct antimicrobial effect. The use of CO_2 is sanitary and completely unobjectionable (1).

Carbon dioxide has been used for more than 50 years in soda-water drinks to prevent microbial growth and to inhibit any precipitation in the bottle. The use of CO_2 is a new application in the pretreatment stage of a water purification system for pharmaceutical use. It is a new technology to clean membrane systems without the use of any chemicals. Processing water with CO_2 is similar to the process in nature when raindrops fall down to earth. As rain falls, water dissolves CO_2 from the air and is then, by trickling through the ground, able to dissolve carbonates in the soil.

This way of pretreatment provides the following advantages:

- Easier and more user friendly to validate as a cleaning process for pharmaceutical Purified Water (PW) systems than the use of chemicals;
- Replacement for softeners that are based on resins, the use of sodium chloride brine, and the elimination of aggressive chemicals for pretreatment;
- Reduction in water consumption normally caused by regeneration of softeners;
- No microbial growth in the water system;
- Pretreatment costs are reduced up to 85%;
- Investment costs are reduced up to 70%;
- Ease of installation, even in case of replacement of an existing softener;
- Environmentally friendly (1); and
- Verification of the removal of the sanitizing agent (CO_2) is easy.

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The method of injecting CO_2 upstream of the RO membrane during shutdown periods inhibits microbial growth within the system. This process has proven itself to be effective in providing a low cost (capital and operational) alternative to softeners in the pharmaceutical and food industry.

Chemical Basics and the Role of CO_2

The presence of free CO_2 dissolved in water has been an undesired circumstance, especially for the water treatment for steam engines, boilers, hot water distribution, and for modern desalination systems.

An important aspect in water purification is the adjustment of the lime-carbonic acid - equilibrium that corresponds with an equilibrium pH-value (pH_s). The divergence of this equilibrium is specified as Langelier Saturation Index (LSI) as shown in Equation 1..

$$LSI = pH - pH_s \qquad \text{Eq. 1}$$

Positive LSI values indicate that the feedwater is depositing lime ($CaCO_3$), which leads to calcination. Negative values indicate that the water is able to dissolve lime.

An LSI of zero is targeted and an effective regulation of this lime – carbonic acid equilibrium can be realized by injecting CO_2 into the water.

Based on the above reason, the injection of CO_2 into reverse osmosis (RO) systems during shutdown periods has two big advantages. The first advantage is removal of scaling, the second, inhibition of microbial growth. The following reactions (Equations 2-4) will occur as CO_2 dissolves in water and its reaction with carbonates. Equation 2 has a slow equilibrium adjustment, while Equation 3 has a fast equilibrium adjustment.

$$CO_{2\,(aq)} + H_2O \longleftrightarrow H^+_{(aq)} + HCO^-_{3\,(aq)} \qquad \text{Eq. 2}$$

$$HCO^-_{3\,(aq)} \longleftrightarrow H^+_{(aq)} + CO^{2-}_{3\,(aq)} \qquad \text{Eq. 3}$$

$$Ca^{2+}_{(aq)} + HCO^{-3}_{(aq)} \longleftrightarrow H^+_{(aq)} + CaCO_{3\,(s)} \qquad \text{Eq. 4}$$

If CO_2 is injected during the shutdown of an RO-system, the pH is lowered. The pH, the negative log of the hydrogen ion concentration, is a measure for the concentration of hydrogen ions (H^+) in a water-based solution. The more hydro-

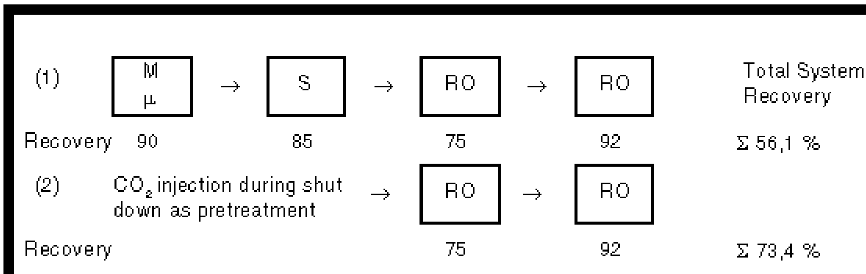

Figure 1. Total recovery of purified water systems with different pretreatment. Note: M = multimedia filter and S = softener.

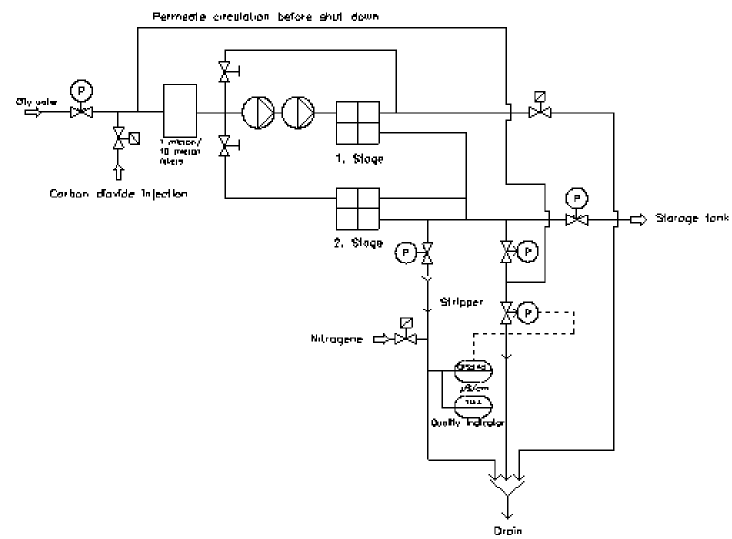

Figure 2. Schematic P+ID of a USP 23 pharmaceutical double-stage RO-system.

gen ions are present, the lower the pH and the more acidic the solution.

For the maintenance of the equilibrium of CO_2 and lime ($CaCO_3$) a certain amount of free CO_2 is necessary. This CO_2-amount causes a corresponding pH-value that is called equilibrium pH (pH_s).

The injection of CO_2 during the RO shutdown shifts the first equilibrium to the right side. The concentration of H^+ ions is increased and the second equilibrium is shifted to the left side towards bicarbonate. The result of this equilibrium can be seen in the third reaction, when carbonates ($CaCO_3$, $MgCO_3$) are dissolved in the RO-system and are finally flushed to drain.

Acidification by the use of CO_2 to lower the pH is very effective and it is possible to control scaling and to work without a softener. Acid addition is well known for (as an example) the cleaning of swimming pools with citric acid. A similar process can be found in the nature, where CO_2, dissolved as carbon acid, has got the ability to dissolve limestone.

Microbial growth must be prevented as much as possible in sanitary RO systems, but there is no absolute microbial safety in water plants (3, 4). The plant operator has many possibilities and techniques to keep the microbial growth down. To reduce bioburden in the water system, the first and most important consideration is sanitary design and the material used (some potential problems for design consideration are threaded connections, polyvinyl chloride (PVC)-piping, resins, and phases of stagnant water). The *United States Pharmacopeia 23* (*USP 23*) 7th Supplement is now concerned with every part of a water system to control the microbial growth.

Because of microbial growth and bioburden experiences with softeners being used in front of a sanitary designed RO system, the aim was not to build the softener in a sanitary design — but to develop a system whereby non-sanitary softeners would not be necessary (5).

In 1994, Letzner introduced CO_2 in the treatment of pharmaceutical water systems (6). In 1996, the use of CO_2 with pressure was used (comparable with a mineral water bottle) for the shutdown of the RO systems. The result was consistently very low bioburden levels. The same low bioburden levels were exhibited even when the RO system was not running during the weekend or on holidays.

The growth of carbonate crystals evolves over a long period of time. All installed RO systems, even those with high carbonate hardness, are running with 80% recovery and show in practice that the shutdown time in combination with pressurized CO_2 is totally sufficient to dissolve any scaling from the RO membrane elements. Before start-up the acidic water and dissolved carbonate salts are flushed to drain (7).

For RO systems that are running day and night a scale sensor is used to detect scaling. The recovery is automatically reduced until LSI is negative and by this process scaling cannot happen. Traditional softeners are running with approximately 85% recovery. The total system recovery of an RO system combined with CO_2 pretreatment is always higher than combined with a softener.

System Design I

Often the following first system design is realized to produce purified water with RO-systems. A multimedia filter and a softener are placed in front of a double-stage RO-system (Figure 1).

The second system design (shown in the bottom of Figure 1) increases the total system recovery up to 73.4%. The multimedia filter and the softener have been replaced by pressurized CO_2 pretreatment. Normal pretreatment systems typically are not designed to remove microbiological growth. The goal of pretreatment is to control the level of bioburden with no increase in microbiological loading. The pressurized CO_2 method fulfills this requirement.

Function of Pressurized CO_2 Pretreatment

During the shutdown, CO_2 is injected into a closed system similar to the hermetically sealed system of the mineral water bottle. The cartridge filters and membrane elements are deadheaded and pressurized with CO_2 to 2 to 4 bar (shown in Figure 2). This lowers the pH to less than 5.5, which inhibits microbial growth in the stagnant water.

Recently, RO plants with permeate recirculation before shut down were designed to take care that low-nutrient water is kept in the plant throughout the shutdown. First of all, a higher volume of CO_2 can be dissolved and the low-nutrient water reduces microbial growth in combination with lowering of the oxygen content and the pH. Based on this mechanism and verified by our experience with many RO plants around the world, an RO system with pressurized CO_2 pretreatment can be shut down without any microbial growth for days, weeks or months.

This aspect is very interesting for the pharmaceutical industry where purified water according the *USP 23* 7th Supplement is needed. Even bulk chemical production requires water according the USP. In some cases, large water capacity is only demanded once a month. This is also a good opportunity to use pressurized CO_2 to retard microbial growth during this long shutdown period.

According to the EG-GMP regulations, the bioburden before, within, and be-

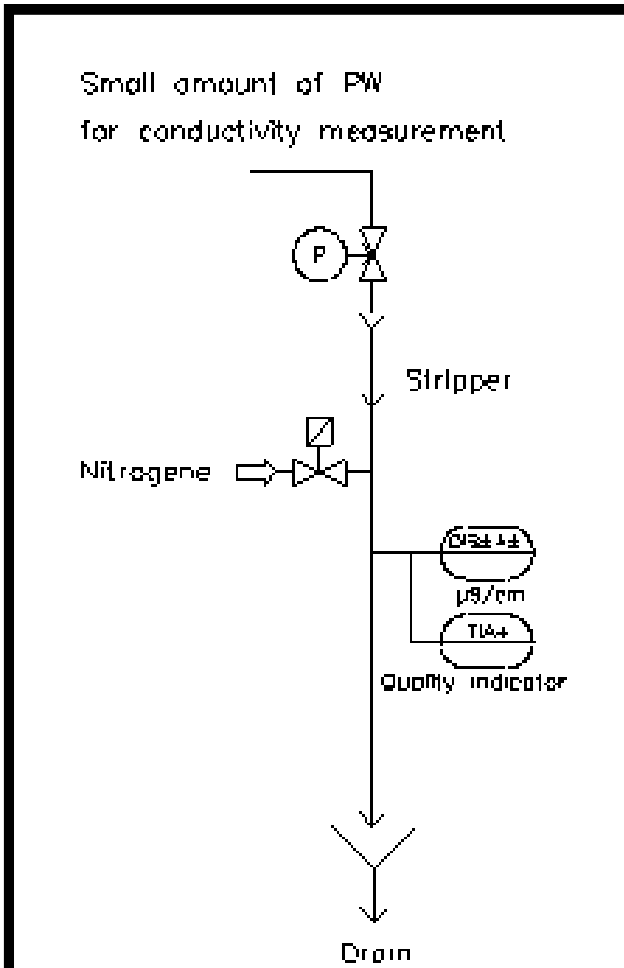

Figure 3. Schematic P+ID of a stripper.

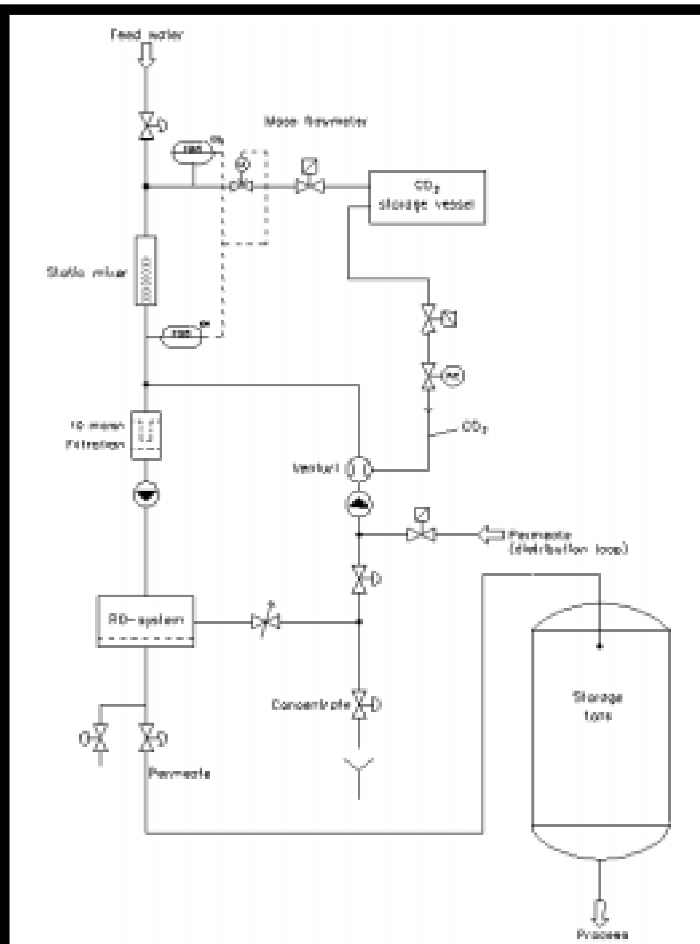

Figure 4. Schematic P + ID of an industrial single-stage RO system for the food industry.

hind the water system should not be increased. All water sample specimens should contain less than 100 colony forming units per milliliter (cfu/mL).

CO_2 and *USP 23* 5th Supplement

The draft version of the Pharmaceutical Manufacturers Association-Water Quality Committee (PMA WQC 4/94) introduced new quality control mechanisms regarding PW, Water For Injection (WFI), and Pure Steam. The wet chemical test has been replaced by conductivity and total organic carbon (TOC)-level control to guarantee the water quality based on ions and organics. Since May 15, 1998, TOC measurements are to be done by a modern technique that replaces the potassium permanganate test for oxidizable substances.

Conductivity measurement should be made without temperature compensation and is diverted into three different measuring stages.

Stage 1: ≤ 1.3 microSiemens per centimeter (µS/cm) (25 °C);
Stage 2: ≤ 2.1 µS/cm (25 °C); and
Stage 3: 2.2 ≤ x ≤ 4.7 µS/cm (25 °C), depending on pH.

According to Stage 1, it is possible to measure the water conductivity continuously. If the water fulfills this value, it meets the requirements of *USP 23*. If the specimen fails, the second stage has to be applied.

In Stage 2, CO_2 dissolved in the water sample must be stirred vigorously into equilibrium with the CO_2 value in the air. If the measured conductivity does not change more than 0.1 µS/cm within 5 minutes, the conductivity can be read from the conductivity meter. If the specimen fails at this stage, the third stage has to be done.

Stage 3 addresses to different CO_2 values in the air, which can exist (e.g., in areas of industrial concentration). Here the conductivity must be measured depending on the pH of the water sample (8).

Finally Stages 2 and 3 of *USP 23* 5th Supplement show how to deal with a higher conductivity caused by CO_2.

System Design II

Traditional water purification systems include PVC-piping, threaded connections, dead legs, non-drainable ball valves, glass fiber vessels, and other entrapment areas in which microbial growth is difficult to control. Generally, European systems are not running continuously 24 hours a day and especially not during the weekend. Water purification plants are mostly based on resin, carbon, and multimedia filters whose components are expensive to build in sanitary stainless steel. Costs will be generated for softener regeneration, multimedia filter, carbon filters, salt tablets, chemicals, and water for backwashing. Brine vessels have to be cleaned regularly.

The pretreatment of a water purification system has to prevent the following:

- Carbonate and sulfate scaling of Ca^{2+},

Mg^{2+}, Ba^{2+}, Sr^{2+};

- Colloidal- and biofouling;
- Fe and Mn precipitation; and
- Oxidation of polyamide (PA)-membrane elements by free chlorine.

Large industrial water systems for seawater desalination and breweries normally will not use a softener in front of an RO-system. Scaling only occurs if the solubility product is reached by concentrating the water in the RO. This process depends on the ionic strength and the pH of the feedwater.

At high pH, (surface water) scaling is more critical. The RO membrane becomes more sensitive to oxidation and iron (Fe), and its lifetime is reduced.

A scaling-programmable logic control (PLC)-software and a scaling sensor could show if any softener or scale inhibitor is needed. For example, if the sensor indicates scaling when the RO system is running continuously 24 hours a day or feedwater is changing, then an amount of a scale inhibitor (5 parts per million [ppm] of HMP or acryl acid) is injected to reach the threshold effect. Qualified systems showed that no dosing chemicals could be found in the PW. Based on conductivity and temperature, a water quality controlled dumping valve makes sure that only water according *USP 23* is fed into the storage tank.

Using this method, starting with drinking water quality, the normally low bioburden and pyrogen-free feedwater is supported by the following:

Sanitary pretreatment, membrane valves, Triclover™ connections, orbital welds, and sanitary booster pumps. These sanitary components are necessary in the pretreatment design to assure there will always be a low bioburden in the system during shutdown periods.

To measure the permeate conductivity according to the first stage of *USP 23*, a special unit has been designed for RO-systems. In a stripping column for a small amount of permeate, the conductivity is measured based on salt passage without the influence of CO_2. Direct injection of nitrogen removes dissolved CO_2 in the permeate, based on partial pressure difference (shown in Figure 3).

CO_2 and ISPE Baseline Pharmaceutical Engineering Guide

Sometimes a degasifier for RO systems is recommended if the feedwater has high levels of CO_2. In some applications, CO_2 is removed by an atmospheric degasifier that is problematic due to its potential of increasing the bacterial burden.

Degasification is unnecessary for pharmaceutical RO systems but it is convenient with multi-effect stills in the production of WFI. Carbon dioxide and oxygen are non-condensable gases that are dissolved within the feedwater and become liberated as the temperature of the water increases. It is necessary to remove these two gases because of their detrimental effects on distillation units. Also, dissolved CO_2 increases the water conductivity.

Traditionally, degasification takes place after the multi-effect still. Sometimes the U.S. Food and Drug Administration (FDA) criticizes such solutions, because the last effect runs at atmospheric pressure to remove the non-condensable gases and only a evaporation temperature of approximately 100 °C can be obtained. A better solution is to degasify the feedwater in front of the effects to get a higher temperature (110 to 121 °C) to run an F-value with the last effect or even to achieve sterilization temperature. Another advantage is in excess pressure that allows feeding the produced WFI into storage tanks located higher than the still.

Consumption of CO_2 for Pretreatment of a *USP 23* PW Double-Stage RO

Results from one customer demonstrated the following advantages: no salt tablets, no brine vessels, no salt transport within the company, and no storage rooms for salt tablets.

At this site, the PW RO system had a production capacity of 1,000 liters per hour (L/h). Its daily water production was 5 cubic meters (m^3); yearly water production was 1,000 m^3. The plant had a yearly CO_2 consumption of three 40 kilogram (kg) bottles. Yearly nitrogen consumption was five 50 kg bottles.

Mechanism of Bacteriostatic Action of CO_2

A lot of different publications are reporting about the research in the bacteriostatic action of CO_2. For example G. J. Haas, et al., were curious why CO_2 has such a specific action against microbes. Luck et. al. found out that *Pseudomonads* appear to be very sensitive to CO_2 (1977) (9).

Daniels et al. (1985) cite four theories for the mechanism of the bacteriostatic action of CO_2.

1. The exclusion of oxygen by replacement with CO_2 many contribute slightly to the overall effect, by slowing the growth rate of aerobic bacteria.
2. The ease with which CO_2 penetrates the cell may facilitate its chemical effects on the internal metabolic processes.
3. Carbon dioxide is able to produce a rapid acidification of the internal pH of the cell with possible ramifications relating to metabolic activities.
4. Carbon dioxide appears to exert an effect on certain enzyme systems. Such effects do not appear to be similar among species, and may well be affected by different growth conditions among members of the same species (10).

Since introduction of the pressurized CO_2 pretreatment, a lot of positive experience has been collected with the operation of RO systems without any softener. More research regarding this method must be and will be done in the future.

In order to implement this pretreatment approach, it is necessary to have CO_2 storage bottles, rooms with sufficient ventilation, and a CO_2 sensor.

Redesign of Existing RO Systems

A very interesting option is to rebuild existing RO-systems, based on softeners, with the patented pressurized CO_2 system (11). A simple technique with little instrumentation is needed to achieve a system running without the brine vessel.

Production of WFI

The USP limits the techniques for production of WFI (compendial WFI) to distillation and RO. Ultrafiltration for the production of WFI is currently not acceptable. The use of RO units for producing WFI is significantly limited to a small percentage of applications in the United States (12). The *European Pharmacopoeia* allows only distillation for producing for WFI, however, ultrafiltration is used to produce WFI-quality (non-compendial WFI) for final rinse of vessels.

More and more hot-water-sanitizable RO units are build to produce compendial WFI. The RO-system is flushed periodically during shutdown with 90 °C hot permeate.

The bulk chemical production for pharmaceutical substances often requires a large amount of water periodically (e.g., once a month) and for some cases the PW should not contain more than 0.25 Endotoxin Units per mL. The use of hot-water-sanitizable RO-systems coupled with CO_2 is an effective way to shut down these systems without increasing the bioburden within the RO system and to keep the endotoxin level below *USP 23* requirement.

In accordance with *USP 23*, the validation of these systems includes a heat distribution study to demonstrate that a temperature of 90 °C is achieved throughout the entire system. This sanitization method is easier to validate than to demonstrate the effective removal of chemical residues after chemical sanitization of the RO system.

Electrodeionization

Electrodeionization (EDI) is an effective method of improving the chemical water quality. Single-stage RO-systems are combined with EDI-systems to produce PW. Pressurized CO_2 in combination with this deionization technique during shutdown achieves a microbial and endotoxin control of these high-purity water systems.

The Use of CO_2 for RO Systems in the Food Industry

In the brewing, beverage, and food industries, it is a common goal to replace the traditional pretreatment for RO-systems with pressured CO_2. Using pressurized CO_2 has become a viable alternative to softeners. It provides a saving of expenses for the wastewater from RO-concentrate and other advantages such as hygiene within RO-systems, low bioburden, and ecology.

With the proviso that only CO_2 is used for pretreatment, often the local authority permits the direct discharge of RO wastewater to the receiving stream, into an injection well or even into a bathing lake, without paying the usual wastewater charges. This means, with charges of Euro 3 to 4 per cubic meter (/m^3) ($3.3 to 4.4/m^3) wastewater, a reduction in operation costs up to 75% is possible.

The reliable run of these plants requires, especially for large industrial applications, a lot of experience and care in design and execution. The following automated process steps are useful for RO-systems.

1. Periodical cleaning with pressurized CO_2 and permeate by recirculation;
2. Preservation of the RO-system with pressurized CO_2 during long shutdown periods;
3. Displacement of RO-concentrate after every shutdown; and
4. Adjusted, careful supervised and controlled (mass flowmeter) injection of CO_2 during production to lower the pH of the feedwater.

The feedwater must meet the requirements of TVO (German Drinking Water Regulation) or of U.S. Environment Protection Agency (EPA) for drinking water, no matter if well water or water of a distribution system is used. Also, the feedwater should be free of iron and manganese, otherwise additional pretreatment steps, such as iron removal, will be necessary.

By courtesy of the company IVA mbH (13), the following examples will show two different systems that are running in the food industry for several years without any softener and pretreatment chemicals. IVA mbH developed this pretreatment and started to apply it very early and successfully. Figure 4 shows the P&ID of those systems.

1. Beverage industry (fruit drinks, mineral water)

RO-capacity: 60 m^3/h; recovery: 80%
normal wastewater charges: Euro 3.25/m^3 (U.S.$ 3.58/m^3) wastewater
CO_2 consumption per m^3 feedwater: 0.15 kg/m^3

Using this kind of pretreatment, the beverage company got the local authority permit to discharge of the RO-concentrate directly and without any costs to the receiving stream.

Yearly cost savings: about Euro 172,000 (U.S.$190,000)

2. Food industry (canned goods, jam, and juice). The entire water supply for product and process water was switched from city water to well water. One part of the water treatment has been an RO-system as noted here.

RO-capacity: 120 m^3/h; recovery: 80%
normal wastewater charges: Euro 4.00/m^3 (U.S.$4.44/m^3) wastewater
CO_2 consumption per m^3 feedwater: about 0.9 to 1.0 kg/m^3

Also, in this case the local authority gave the permit to discharge the waste water to the receiving stream.

Yearly cost savings: about Euro 354,000 (U.S.$390,000)

Hope for the Future

The hope for the future is to replace as many softeners in front of purified water systems to minimize the well-known problems of bioburden and microbial growth in RO systems caused by softeners. Pretreatment against scaling can be fulfilled through pressurized CO_2 and is an easy and effective way to by-pass the above problems. The use of CO_2 should be understood as a very effective and workable method for both American and European Pharmaceutical water applications.

Summary

According the *USP 23* 7th Supplement each pharmaceutical purified water system should have microbial control before, within and after the system. This article introduces possibilities for consideration of a new application, pressurized CO_2 pretreatment, which will provide the kind of control required as well as being in concert with environment protection and over all operational costs.■

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Glossary

cfu: colony forming units

EPA: U.S. Environment Protection Agency

LSI: Langelier Saturation Index

pH_s: equilibrium pH

PLC: programmable logic controller

PMA WQC: Pharmaceutical Manufacturers Association Water Quality Committee

TOC: Total Organic Carbon

TVO: German Drinking Water Regulation

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