Innovative PW-/HPW-Production for Pharmaceutical Industry

Process Optimization by New Continuous Sanitizing Technology

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The production of Purified Water (PW) and Highly Purified Water (HPW) represents one of the most important processes in pharmaceutical industry. Reducing corresponding cost is therefore a widespread topic in that branch. The innovative SANITRON technology has been designed with efficiency in mind, based on a sophisticated combination of high quality equipment. Softened water already before entering the membrane stage is continuously sanitized, with CO_2 removal and chlorine reduction taking place simultaneously. Long time tests have been carried out, which demonstrate that supplementary sanitizing procedures in membrane or EDI stages are normally not necessary.
For this reason, this method manages without addition of chemicals. As the efficiency is increased to up to 90%, consumption of energy and drinking water is considerably lowered. The environment-friendly basic principle is furthermore supported by an incontestable minimization of the waste water volume. Due to the reduced number of operating steps, the availability of the plant is enhanced - compared to conventional systems, shutdowns have to be expected only rarely. The technology has been implemented in the new OsmoVision plant. This article presents a summary of the current state of the art, detailing several advantages of this new approach.

1. State of the Art in the Production of PW/HPW

■ Feed-Water Pretreatment

For the production of PW/HPW, the pharmaceutic industry currently uses multi-step procedures combining several methods: The initial step usually consists in pre-filtration to separate coarse contaminations (suspended matter, particles) from the drinking water, whereas substances responsible for the hardness of the water (mainly Mg^{++} and Ca^{++} ions) are removed in a softening process.
Generally this latter step is carried out as an ion exchange sequence, by means of cation exchange in the form of sodium. In order to minimize the hardness gap, often two ion exchanger columns are connected in series.

■ Demineralization by Reverse Osmosis

The preparation described above is followed by a reverse osmosis as a membrane step, used to demineralize the water and to retain germs. The efficiency of single-stage reverse osmosis amounts to ca. 70-75% yield in permeate. To improve this result, the concentrate may be processed in a second reverse osmosis step (called RO concentrate step), which is able to increase the efficiency to 90%.

■ Final Conditioning by Electro-Dionization

During the final step, the water flows through a diluate chamber filled with ion exchange resin. By means of a constant potential present at the electrodes, contained ions (e.g. sodium or chloride) are transmitted through ion-selective membranes to a concentrate chamber and washed away in a concentrate stream. This method is called electro-deionization (EDI-process).
A sufficient ionic conductibility inside the concentrate chamber supports the demineralization. To this purpose, neutral salt may be added at the concentrate side, and the concentrate inside its chamber may be recirculated. This way the concentration of separated ions is increased, or the chamber is filled with ion exchanger resin.
As an example, fig. 1 shows the principle diagram for the electro-

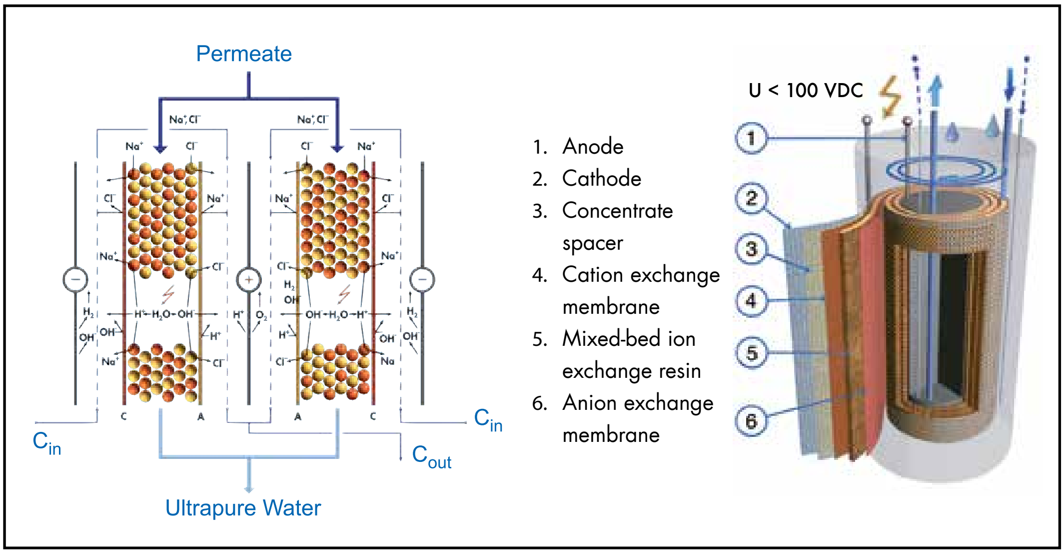

Fig. 1: Elementary diagram and structure of electro-deionization for a helical winding module (SEPTRON®-Module); Source: All illustrations BWT Pharma & Biotech GmbH, if not specified otherwise.

deionization of a helical winder module (SEPTRON®-Module). Results achieved by this method prove to be in conformity with the limits stated by common pharmacopoeia (e.g. EP, USP).

■ Removal of CO_2

An increased CO_2 content in the feed-water often requires a distinct treatment to be performed. Methods frequently used are NaOH metering or membrane degassing. The latter option usually is integrated in the permeate stream of the reverse osmosis stage.

The described combination of procedures meets or even exceeds the requirements with respect to PW and HPW of common pharmacopoeia (e.g. EP, USP acc. to table 1). Water qualities with a conductance of < 0.1 µS/cm, < 20 ppb TOC may be achieved; microbiologic and endotoxin limits (for HPW) are respected as well.

As a core, the presented innovation includes the SEPTRON®-Module for electro-deionization, the only EDI module with helical winding developed in Europe. This way an excellent removal of residual minerals, as well as a considerable reduction of CO_2, SiO_2 and TOC are ensured. A high degree of regeneration is obtained due to the homogeneous electric field. Further benefits offered are the low voltage (<100 V) and a compact design. The two-chamber design ensures

■ Table 1

Requirements according to USP* und EP**

Purified Water			
Parameter	**Unit**	**USP**	**EP (Bulk)**
TOC	ppm C	0.50	≤ 0.50
Conductivity	µS/cm@20°C	–	≤ 4.3
Conductivity	µS/cm@25°C	≤ 1.3	–
Nitrate (NO_3)	ppm	–	≤ 0.2
Heavy metals	ppm as Pb	–	≤ 0.1
Aerobic bacteria	CFU/ml	≤ 100	≤ 100
Highly Purified Water			
Parameter	**Unit**	**USP**	**EP (Bulk)**
TOC	ppm C	n. c. st.	≤ 0.50
Conductivity	µS/cm@20°C	n. c. st.	≤ 1.1
Nitrate (NO_3)	ppm	n. c. st.	≤ 0.2
Aerobic bacteria	CFU/100 ml	n. c. st.	≤ 10
Bacterial endotoxins	I.U./ml	n. c. st.	≤ 0.25

* current United States Pharmacopeia
** current European Pharmacopeia

n. c. st. = no comparable standard

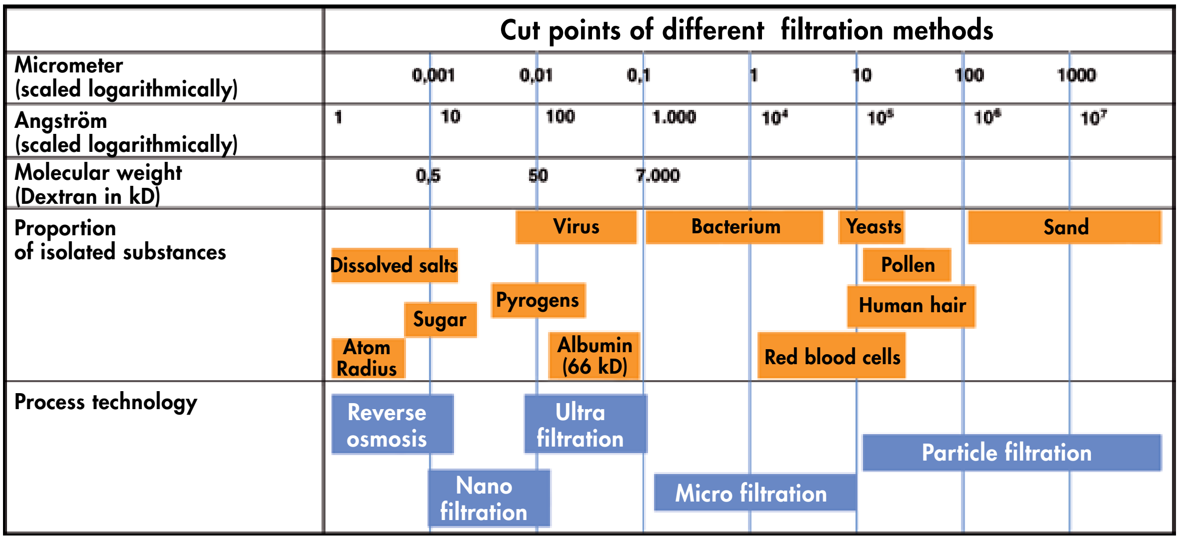

Fig. 2: Cut points of different filtration methods (Source: http://de.wikipedia.org/wiki/Membrantechnik).

optimized hydrodynamic properties, so that the module is characterized by excellent microbiological diluate purity.

2. The SANITRON-Technology

The target of this new development consisted in improving the results of known water conditioning methods, by means of a combination of electro-deionization and membrane separating stages, particularly with respect to the yield of water. Reutilization of substances in the stream by means of the SEPTRON®-Module was another objective.

The membrane separating stages are composed of a reverse osmosis (RO) as the first and a nanofiltration (NF) as the second step. This means that, the concentrate delivered by the reverse osmosis is fed to the nanofiltration step. Due to the higher cut point of nanofiltration (fig. 2), the conductibility for the resulting permeate stream and for the feed-water are identical, so that the permeate in the form of a concentrate stream can directly be supplied to the EDI Module – dispensing with the need for artificially increasing its conductibility by supplementary measures.

As described above, the conventional approach requires further elements (addition of neutral salt, recirculation, use of ion exchanger resin) for that purpose.

For this reason, this innovation represents a significant progress in water treatment, since filling the concentrate chamber of the EDI Module with ion exchanger resin increases the pressure loss in the concentrate chamber as well as the microbiological risk, particularly in the case of laminar flow past plates (for plate EDI Modules).

A certain portion of the remaining concentrate of the nanofiltration step is rejected; the rest is recirculated as follows: The concentrate stream leaving the SEPTRON®-Module passes a reaction and degassing vessel, the SANITRON reactor (see fig. 4) before reentering the feed-water stream at the inlet of the membrane stage.

■ Efficiency

As mentioned beforehand, this innovation recirculates the concentrate resulting from electrodeionization and partially also from nanofiltration, and delivers it back to the feed-water stream.

In contrast to conventional PW and HPW production by single stage reverse osmosis with a total efficiency of 65-75%, the new patented SANITRON process[1)] is able to reach a value of 90%.

■ Degassing

Another possible problem has been taken into consideration as well: The concentrate issuing from electro-deionization may contain dissolved gas, e.g. hydrogen (H_2) and oxygen (O_2), as well as oxidation products, e.g. hydrogen peroxide (H_2O_2) and chlorine (Cl_2), originating from the electrode reaction. These substances may damage the membranes of the membrane stages downstream. The reactor solves this problem by extraction of gaseous components, targeted mutual reaction of oxidation products, and elimination of the excess by a catalyzer installed downstream. At the electrodes of the EDI-Module, mainly the following reactions take place:

Anode:

- $2\ H_2O \rightarrow O_2 + 4\ H^+ + 4\ e^-$
- $2\ Cl^- \rightarrow Cl_2 + 2\ e^-$
- $O_2 + ½\ O_2 \rightarrow O_3$

Cathode:

- $2\ H_2O + 2\ e^- \rightarrow H_2 + 2\ OH^-$
- $O_2 + 2\ H_2O + 2\ e^- \rightarrow H_2O_2 + 2\ OH^-$

The common supply of recirculated concentrate together with softened feed-water enables degassing of the feed-water to be performed at the same time. The streams entering the reactor are guided through unary nozzles. The spraying procedure delivers finest nebulized droplets with maximum surface for liquid-gas transition, thus speeding up the expulsion of dissolved gas.

The efficiency of this step is furthermore enhanced by injection of air. By fine tuning of the spraying procedure, of air distribution inside the reactor and of the relation between air-flow to water supply, a value of up to 80-90% for CO_2 is achievable (fig.3). This way supplementary steps (e.g. membrane degassing or NaOH metering), can be omitted.

1) Patent Specification: Method and plant for water conditioning, Pub. No.: WO/2013/174628; International Application No.: PCT/EP2013/058915.

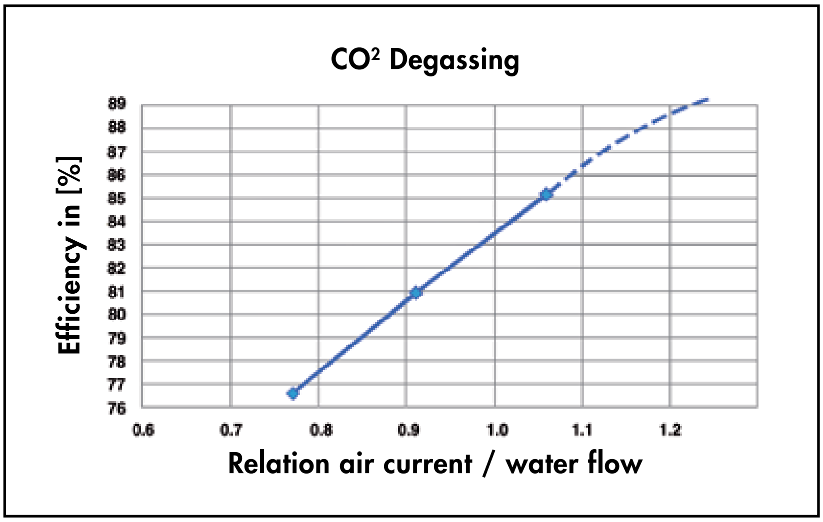

Fig. 3: Efficiency of CO_2 degassing depending on the relation air current / water flow for a CO_2 concentration of 50 ppm in water.

An outstanding efficiency is also ensured for removal of hydrogen. As this results amounts to 99%, the hydrogen unavoidably produced during the EDI process, is reliably extracted.

■ Removal of Cl_2

The hydrogen peroxide (H_2O_2) excess formed at the concentrate side of the SEPTRON®-Electrodeionization Module (according to the electrode reaction presented above) can be used to reduce the free chlorine contained in the feed-water. This is sufficient for a concentration of up to 0.5 ppm of free chlorine (Cl_2), so that in these cases conventional chlorine reduction stages (e.g. addition of sodium bisulphite, charcoal absorbers, UV oxidation) can be left out.

In the SANITRON reactor, the free chlorine (Cl_2) in the feed water disappears completely, as it reacts with the hydrogen peroxide (H_2O_2) delivered by the concentrate stream as follows:

Reactions: H_2O_2/Cl_2

- $Cl_2 + H_2O \rightarrow HCl + HOCl$
- $HOCl \rightarrow OCl^- + H^+$ (pK_a=7.53)
- $OCl^- + H_2O_2 \rightarrow Cl^- + H_2O + O_2$

The SEPTRON®-Module with helical winding has proved to be perfectly appropriate for that purpose. Due to its inner structure, it is possible -by an adequate flow- to produce supplementary oxygen at the anode inside the concentrate chamber, thus increasing the hydrogen peroxide (H_2O_2) content. This positive effect is supported by development of new materials for the electrodes.

■ **Continuous Self-Sanitizing**

An additional useful consequence of the presence of oxidation products like hydrogen peroxide (H_2O_2) and free chlorine (Cl_2) in the recirculated concentrate stream is the continuous sanitizing of the feed-water. As both streams are continuously mixed inside the SANITRON reactor (fig. 4), the number of germs in the feed-water is reduced, so that additional sanitizing measures for membrane or electro-deionization stages are normally not necessary.

■ **HPW-Quality by Ultrafiltration Membrane Unit**

In order to ensure HPW quality according to the most demanding standards, the SANITRON method can be combined with the patented SEPTRON®-BioSafe EDI-Module, acting as an additional process step and germ barrier. The integrated ultrafiltration membrane unit meets all requirements for the safe production of super-clean water in pharmaceutic PW and HPW quality, also with respect to microbiological limits for HPW. This unit can simply be exchanged in the course of usual service, so that the prescribed sterility is permanently maintained.

■ **Analysis of Measuring Results**

Results of field tests relating to the germ load in PW/HPW production plants based on the SANITRON technology are presented in the following illustrations. Fig. 5 shows cfu values in reverse osmosis permeate and in EDI diluate (purified water) at the exit of the electro-deionization step of a PW production plant, featuring the new technology and a SEPTRON®-EDI-Module. Microbiological requirements for PW are met already after the reverse osmosis step; at the exit of the EDI step the results reliably fall below the corresponding limit.

Fig. 6 contains results of a long-time field test in a HPW production plant, which was equipped with the new technology including SEPTRON®-BioSafe EDI-Module with integrated ultrafiltration membrane unit.

Also in this case, cfu values at the exit of the reverse osmosis stage already correspond to the microbiological requirements

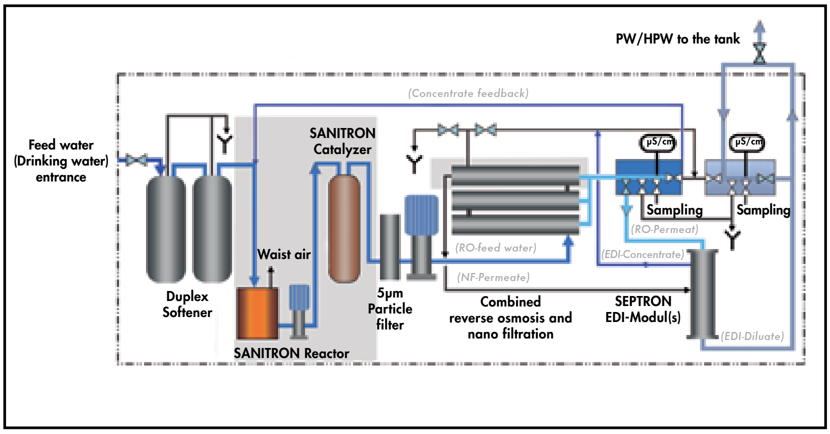

Fig. 4: Elementary diagram of the SANITRON-Technology.

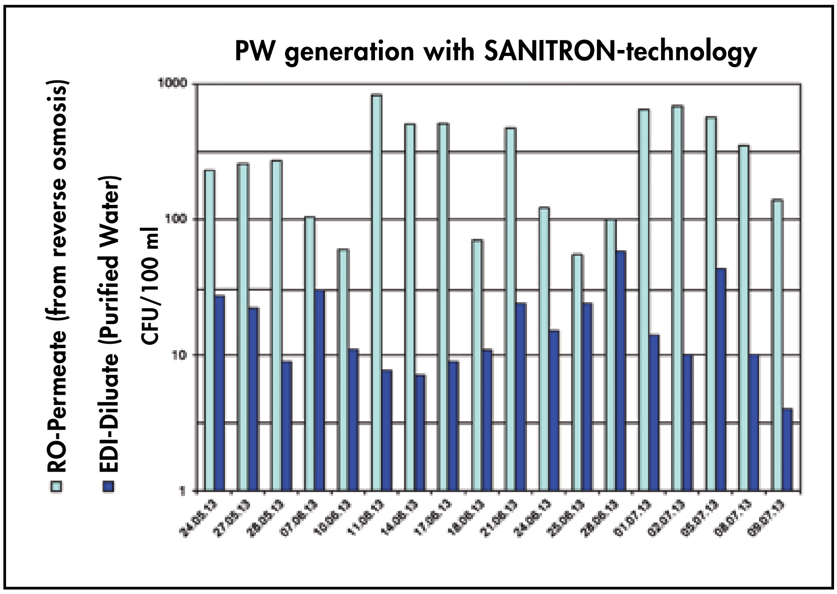

Fig. 5: Cfu values in RO-Permeate and EDI-Diluate (Purified Water) of a PW production plant equipped with SANITRON-Technology (with SEPTRON®-EDI-Module, without BioSafe-Ultrafiltration-Membrane Unit).

valid for Purified Water. After the passage through the electro-dionization stage with ultrafiltration membrane unit, no colony forming units in the EDI diluate could be detected at all, in the course of the complete duration of the test. HPW quality is continuously guaranteed.

Further examinations have been carried out, all of them with the same result: The SANITRON technology is able to reduce the cfu loading in a plant to a constant low level, and additional sanitizing measures for membrane and electro-deionization stage are normally not required.

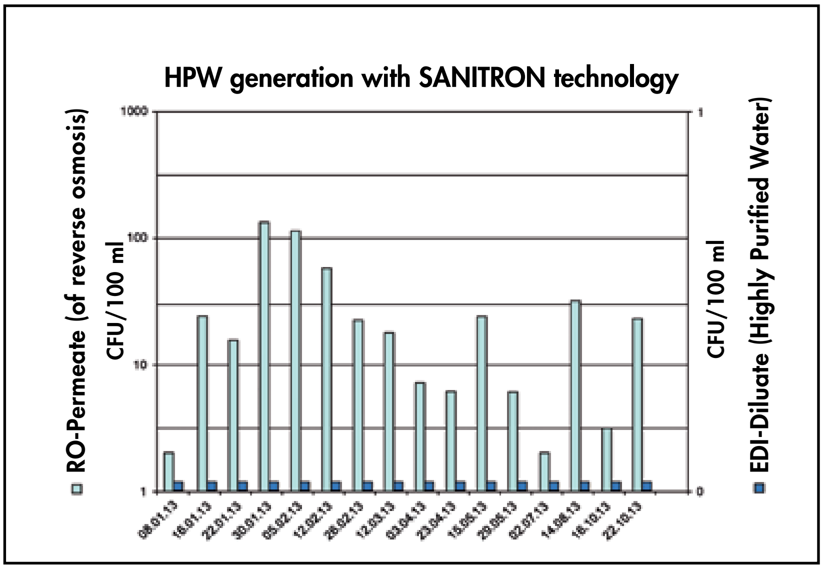

Fig. 6: CFU values in RO-Permeate and EDI-Diluate (Highly Purified Water) of a HPW production plant equipped with SANITRON-Technology (featuring SEPTRON®-BioSafe EDI-Module).

■ SANITRON Catalyzer

To protect the membrane stage located downstream, remaining oxidation products, e.g. hydrogen peroxide (H_2O_2), are extracted by a catalyzer at the exit of the reactor. Platinum or palladium catalyzers, manganese dioxide or charcoal are admissible in this environment. The presented example includes a catalyzer on manganese dioxide basis.

3. Benefits of the new technology

Compared to conventional PW/HPW production methods, plants equipped with the new SANITRON technology dispose of several important advantages:

- The total efficiency of a plant may be increased from usual values of 65-75% to 90%, depending on quantity and quality of feed-water used – without additional process steps.
- For CO_2 degassing, the efficiency is usually in a range between 80 and 90%, saving expenses for additional steps like membrane degassing or NaOH metering.
- Free chlorine in a concentration of up to 0.5 ppm can be extracted without supplementary equipment (addition of sodium bisulphite, charcoal absorbers, UV oxidation).
- Feed-water in the reactor is continuously sanitized. Due to this systematical reduction of the number of germs, corresponding measures in membrane and electro-deionization stages are not required.
- Due to the absence of hot water sanitizing with corresponding cooling process, energy consumption is lowered.
- As these additional sanitizing steps are omitted, the thermal and chemical stress is reduced. This extends the lifetime of parts like seals and membranes.
- The increased efficiency automatically reduces the consumption of drinking water and the volume of sewage. This represents not only an important aspect with regard to cost, but also to environment protection.
- Reduced number of interruptions.
- Affordable investment cost with considerable economy with respect to running expenses.

2) Water Passion, Customer Magazine of Best Water Technology Group, 2014/2015, page 52–54: „Pure Water for High Tech Industry".

4. Implementation of the Technology in a Standardized Plant Design

The SANITRON technology together with the SEPTRON®-EDI-Module can be integrated into a PW/HPW production plant in no time. To implement the system in a standardized plant design, the skid style is a method nowadays frequently used. The skid construction offers several advantages:

- All process steps including the control are completely pre-assembled on a frame, ready to operate.
- This way the system can be pre-tested and pre-qualified already at the site of the manufacturer.
- A complete Factory Acceptance Test (FAT), carried out in conformity with real operating conditions, can be performed by the manufacturer as a part of the IQ/QQ phase of the qualification.
- The system is delivered in state ready for connection, so it can be installed at once. The compact design simplifies in situ integration as well.
- As the manufacturer undertakes the responsibility for the entire preparation, all steps from installation, start-up and test up to qualification do not take much time.
- Standardized available features e.g. online residual hardness measurement can be completed upon need.
- The user-friendly software is validated and can quickly be integrated into the system. Option packages for automation (data filing, analysis, audit trail and data export) are available upon request.

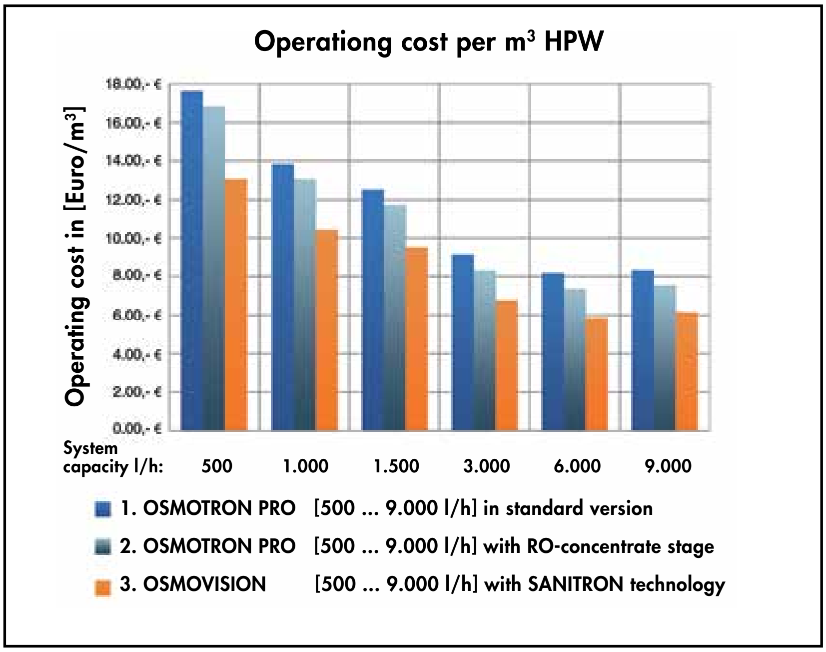

Fig. 7: Comparison of specific operating cost per m³ Highly Purified Water.

5. Cost Assessment

The comparison of a PW/HPW production system featuring SANITRON technology to a conventional system equipped with similar process stages to achieve an identical capability shows the superiority of the SANITRON particularly in the range between 500 l/h to 9 000 l/h. Cost reduction amounts to 4 to 10%.

In the following calculations, operating costs have been evaluated on the basis of different examples with respect to size and plant design.

The following configurations have been compared:

- Conventional PW/HPW production plant, hot sanitization, with membrane degassing and addition of sodium bisulphite (example: OSMOTRON® PRO HPW-2S[2)])
- Conventional PW/HPW production plant, hot sanitization, with membrane degassing, addition of sodium bisulphite and RO concentrate stage for increased efficiency (example: OSMOTRON® PRO HPW-2S[2)]
- PW-/HPW-production plant with SANITRON-Technology (example: OsmoVision[2)])

Six different sizes in the range from 500 to 9000 l/h (PW resp. HPW production, see fig. 7), frequently encountered in pharmaceutic industry, have been assessed.

The comparison has been performed on the basis of the following assumptions:

- Production hours per day: 8
- Working days per week: 5
- Weeks per year: 50
- Electricity costs: 0,11 Euro/kWh
- Regenerating salt: 0,32 Euro/kg
- Drinking water: 1,25 Euro/ m^3
- Sewage: 1,90 Euro/m^3
- Compressed air: 0,13 kWh/Nm^3

In the conventional plants, one hot sanitization was supposed to be performed per month. A lifetime of three years was taken into consideration for the essential wearing parts RO membrane, EDI and membrane degassing module.

As expected, the comparison (fig. 7) shows a decline of the specific production cost (per m^3 of purified water) with increasing plant capacity. The slight rise in the range from 6000 l/h to 9 000 l/h may be caused by the increased power consumption of the pump and by the softening process requiring a high frequency of regeneration.

The result for the plant configuration however is clear: Conventional systems entail major operating expenses, lowered for conventional systems with increased efficiency. Thanks to the optimized total efficiency, DHP/HPW production by plants equipped with the SANITRON technology, delivers the best result.

For a typical plant capacity of 6 000 l/h, the cost advantage of the system OsmoVision 6000, compared to OSMOTRON® PRO 6000 HPW-2S, amounts to 29 600 Euro in the course of the first year – this represents an indisputable argument for the new SANITRON technology.

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