Increasing the Sustainability of Pharmaceutical Grade Water Production

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Dedicated to Prof. Dr.-Ing. Peter Czermak on the occasion of his 65th birthday

Water serves for the production of pharmaceutical ingredients, intermediates and final products. Accordingly, the quality requirements are particularly high. Next to quality, sustainability of the production and climate change mitigation will play an increasingly important role. For instance, in 2015, the total global emissions of the pharma sector was significantly higher than the CO_2 emissions generated by the automotive sector. Thus, efforts must be made at all stages of production of pharmaceuticals to reduce the environmental impact.

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1 Introduction

The health sector is a boon and bane. Its mission is protecting and promoting health, but it contributes to environmental pollution and enhances the climate crisis – which in turn are the major direct or indirect health threats of the 21st century. In 2019, the health sector was responsible for 4.4 % of global net greenhouse gas emissions (2 Gt of carbon dioxide equivalent) [1].

Water is one of the most frequently used raw materials in the pharmaceutical industry. It serves for the production of pharmaceutical ingredients, intermediates and final products, as well as for cleaning and sterilization purposes. Depending on the application, different grades of water quality are required that are defined by current regulations, e.g., the European Pharmacopeia (Ph. Eur.) [2] in the European Union and the United States Pharmacopoeia (USP) [3]. The pharmacopeias set official quality standards in terms of several physical, chemical, and microbiological parameters [4] and ensure the absence of harmful contaminants and impurities in the final products.

The pharmacopoeias allow drinking water as a raw material for the production of water for pharmaceutical use (WPU). According to the European Commission [5], the drinking water quality should at least meet the guidelines of the World Health Organisation (WHO) for drinking water quality.

The two primary water types of WPU are purified water (PW) and water for injection (WFI).

According to the European Pharmacopoeia, following grades of purified water are distinguished:

– Purified water (Aqua purificata): manufacturing of drugs that do not need to be sterile or pyrogen-free.
– Highly purified water (HPW) or aqua valde purificata): manufacturing of drugs that need high biological quality water.

Water for injection (aqua ad iniectabilia) represents the highest quality of pharmacopeial WPU [6]. As it is pyrogen-free [7], it serves for the manufacturing of drugs for parenteral use whose solvent is water [2].

According to Strade, in the pharmaceutical industry steam may be used as plant steam, chemical-free steam, and pure steam. Each of the applications requires different feed water quality and procedures for steam generation [8]. For example, pure steam is gaseous WFI and is used for sterilization, drying and air humidification.

Tab. 1 depicts the quality standards of water for pharmaceutical use (WPU) according to the European and US American pharmacopeias. As can be seen, the principal difference between PW and WFI is the allowable amount of bacterial contamination and the endotoxin level. Endotoxins (pyrogens) are parts of the cell wall of gram-negative bacteria [9].

The preparation of water for pharmaceutical use is among the most energy intensive steps in the pharmaceutical industry [10]. The term "water-energy nexus" highlights the need to examine the use and management of both resources together, as is depicted in Fig. 1.

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Table 1. Quality standards of water for pharmaceutical use (WPU) according to the European and US American pharmacopeias.

Parameter	Ph. Eur.		USP	
	Purified water PW	Water for injection WFI	Purified water PW	Water for injection WFI
TOC [$\mu g\,L^{-1}$]	< 500	< 500	< 500	< 500
Conductivity [$\mu S\,cm^{-1}$]	≤ 4.3 @20 °C	≤ 1.1 @20 °C	≤ 1.3 @25 °C	≤ 1.3 @25 °C
Nitrate [$mg\,L^{-1}$]	≤ 0.2	≤ 0.2	NA	NA
Heavy metals [$mg\,L^{-1}$]	≤ 0.1	NA	NA	NA
Aerobic bacteria [CFU 100 mL^{-1}]	≤ 10 000	≤ 10	≤ 10 000	≤ 10
Endotoxins [I.U. mL^{1}]	NA[a)]	≤ 0.25	NA	≤ 0.25

a) not applicable.

Although it is essential for the pharmaceutical industry to cope with the current quality and safety parameters, there is a strong need for maximizing the energy and water efficiency of this industrial branch in the coming decades [8, 11]. For example, in 2015, the total global emissions of the pharma sector were about 52 Mt of CO_2. This was significantly higher than the CO_2 emissions generated by the automotive sector in the same year [1]. Thus, efforts must be made at all stages of production of pharmaceuticals to reduce the environmental impact.

Sustainable production in the pharmaceutical industry involves the creation of high-quality medical goods using processes that are non-polluting, material- and energy-efficient, and conserving natural resources. Accordingly, future technical solutions demand a holistic approach [12, 13].

Fig. 2 depicts the various and partially contradictory requirements for sustainable production of WPU. Within the depicted requirements, zero liquid discharge (ZLD) is a relatively new approach to eliminate liquid waste solutions and to maximize water usage efficiency [14].

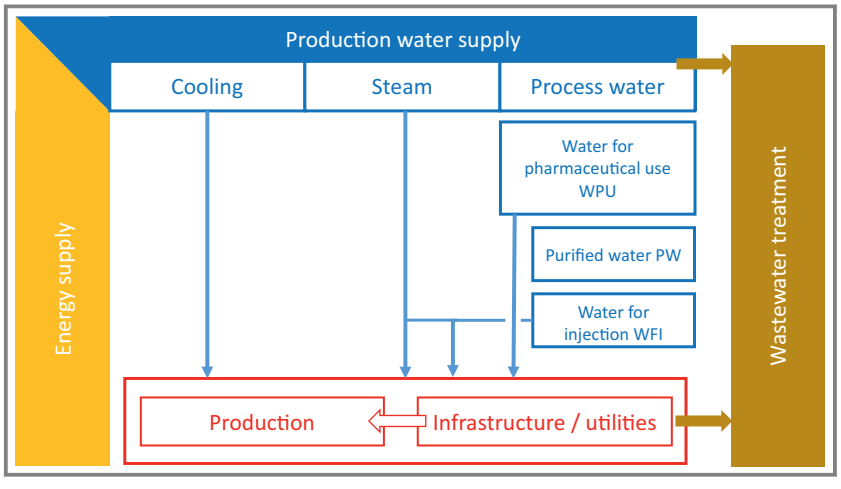

Figure 1. Water energy nexus in the pharmaceutical industry.

2 Production of Water for Pharmaceutical Use

The selected treatment technology is mainly depending on the regulations defined by the pharmacopeias, the desired WPU quality and the cost structure. The production of water for pharmaceutical use is restricted to several qualified technologies including distillation, reverse osmosis (RO), ion exchange (IX), electrodeionization (EDI), and ultrafiltration (UF) [15].

2.1 Established and Qualified Technologies

There is no discussion of alternative techniques in the production of PW and HPW: This is where the membrane processes are established [16]. Initially, distillation of feed water was the exclusive method for the production of WFI in Europe. Since 2017, Ph. Eur. accepted also membrane-based techniques for the purification of water [17].

2.1.1 Distillation

In this process, water is heated until it turns into steam. The low contaminated steam is then condensed back into water in a separate condenser. Two different distillation methods can be distinguished in WFI production: multiple effect (ME) and vapor compression (VC) distillation. Unlike ME plants, VC plants require only a relatively simple and inexpensive pretreatment.

VC distillation has a smaller energy demand, as it is operated at ambient temperature and uses an internal heat recovery. Due to the lower operating temperature, VC plants are less susceptible to scaling and corrosion [18].

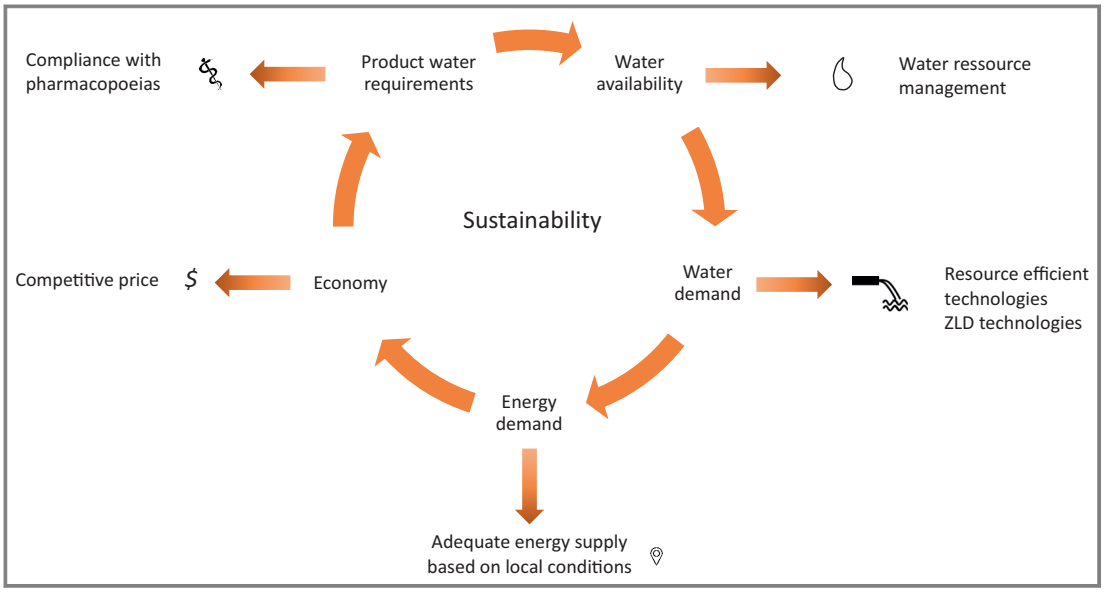

Figure 2. Requirements for sustainable production of pharmaceutical grade water.

The inherent microbiological safety of ME distillation is a feature that membrane processes cannot provide, as it can be classified as self-sanitizing due to the high temperature range [16]. Cataldo et al. stress that this is the reason why Japanese biomanufacturing companies generate WFI only by distillation (hot production), regardless of the pharmacopoeia. They add that also in Europe the majority of companies produce WFI via distillation [17]. However, aerosols may be formed during distillation that may carry non-volatile water components such as salts, organic compounds or microorganisms into the product water. For this reason, the entrainment of droplets must be avoided using aerosol separators.

Another advantage is the adjustment of the desired product flow between 50 and 100 % of the performance. However, distillation is an energy- and cooling-water-intensive process. Therefore, in larger technical systems heat exchangers and compressors are combined with the evaporator to save energy and cooling water [19].

As a rule of thumb, one more distillation stage in ME distillation means approx. 10 % more investment, based on the basic plant price [16].

2.1.2 Ion Exchange

In IX systems, undesirable feed water cations and anions are exchanged reversibly, stoichiometrically and electroneutrally with desirable cations and anions that are attached to the positively or negatively charged functional groups of ion exchanger beads. IX is operated batchwise: When the capacity of the ion exchanger material is reached, regeneration is required to restore the initial state of the material. Regeneration generates salt-containing wastewater.

Often, mixed-bed IX units are placed downstream of cation and anion units to achieve a higher water purity. A mixed-bed unit consists of thoroughly mixed cation and anion resin beads [20].

2.1.3 Ultrafiltration

In UF, porous membranes are applied that retain particles larger than the maximum pore diameter, while particles that are smaller can pass through. UF membranes have the ability to remove suspended matter, bacteria and viruses; dissolved solids are not rejected by the membrane. The driving force for material transport in UF is an applied pressure in the range between 1–10 bars. The typical yield of UF systems treating tab water is about 90 %. UF is considered a good application prior to VC distillation. Flux decrease due to fouling can be overcome to a certain extend by backwashing of the membranes [21].

2.1.4 Reverse Osmosis

In RO, dense membranes are applied that remove dissolved ions, bacteria, viruses and suspended solids. To overcome the osmotic pressure and the resistance of the dense membrane, a pressure significantly higher than in UF is required. The desired volume flow can be adjusted, e.g., by a frequency converter at the high-pressure pump. The typical plant setup includes pretreatment and a combination of single pass RO/EDI/UF. Compared to VE and ME distillation, all the membrane processes inhibit a significantly smaller energy demand.

Variants to the basic RO/EDI/UF design may include the use of ozone, ultraviolet light, double pass RO instead of a single pass, and other components [18].

Herold comes to the conclusion that membrane separation systems based on RO and EDI offer capital and operating cost advantages over ME distillation systems, but not

necessarily over VC distillation systems. Higher overall costs over time especially result from membrane replacement and manpower [18].

2.1.5 Electrodeionisation

In EDI, a combination of thoroughly mixed anion and cation exchange resin beads and ion-exchange membranes are placed in a direct current electric field. The design allows to continuously deionize water without the need for regeneration chemicals, as the cation and anion exchangers are regenerated in situ electrically. Thus, disposal of spent regenerants is avoided. Accordingly, EDI technology can be an efficient and cost-effective alternative to mixed-bed IX [20].

Tab. 2 depicts the features of technical principles for the generation of WPU.

Table 2. Primary treatment processes for the generation of Water for Pharmaceutical Use (WPU) [7, 19, 22].

Technology	Process Description	Advantages	Disadvantage	Environmental impact
Distillation	Evaporation of water and subsequent condensation of the generated water vapor in a separate condenser. Many contaminants remain in the boiling vessel.	– Continuous hot thermal process – Includes removal of gases – Inherent microbiological safety	– Traces of contaminants carried into the condensate. – Energy demand for heating and high cooling water – Careful maintenance required to ensure purity – Brine formation – Fouling/scaling – Steam demand represents the biggest cost contribution – For the production of WFI, supply of the distillation plant with qualified PW required – Larger footprint	ca. 105 kWh m^{-3}
RO	Due to an applied hydraulic pressure (ca. 5.5 to 8.3 MPa), pure water permeates through the dense membrane structure; particles > 200 Dalton (including ions and pyrogens) are rejected	– Rejection of practically all particles/ions, bacteria and organic compounds > 200 Dalton molecular weight (including pyrogens) at a rate close to 99 % – Continuous process – Energy recovery (turbines, pressure exchangers)	– High pressure demand has an impact on operating costs and carbon footprint – Low flow rates per surface unit may require the installation of either large membrane surfaces or intermediate storage tanks to satisfy user demand – Higher risk of microbial contamination – Adequate pretreatment required to avoid rapid membrane scaling ($CaCO_3$ deposits on the surface), fouling (deposits of organics or colloids on the surface) or abrasion (hard particulates) – Management of the wastewater (brine) required	– ca. 2–3.5 kWh m^{-3} product or 6 kWh m^{-3} raw water – 2.1–3.6 kg CO_2 m^{-3} of treated water
IX	Substitution of one kind of ion (regenerant) by another ion (contaminant) on resin beads	– Low energy process – Easy to operate/control – Long lifetime of resins	– Batch process – Frequent regeneration required – Storage of regeneration agents required – Management of the wastewater (brine) required – Only ions can be removed	
CDI	Combination of IX and electrically driven membrane technology	– Continuous process – Very high purity: TDS < 1 ppm – Compact setup – Continuous regeneration of ion exchangers – Low chemical consumption – No waste liquid, no chemical regeneration	– Requires adequate pretreatment (incl. RO) – Only ions can be removed – High investment costs – Electricity required	– 1.65 kWh m^{-3} product (50 $m^3 d^{-1}$ plant) – Nexed^{TM} EDI Technology] – 1.5 kWh m^{-3} (10 000 Lh^{-1})

There are several approaches how to improve the energy demand of existing technologies, such as [17, 23, 30]:
- reducing heat losses of distillation plants,
- heat recovery from wastewaters in distillation plants,
- adjustment of the required water temperature at the point of use,
- increased overall yield of RO plants,
- reducing the amounts of wastewaters that need treatment,
- introduction of new technologies.

2.2 Introduction of New Technologies

Membrane distillation (MD) is a hybrid process based on vapor pressure differences between the feed and distillate side of porous membranes [24]. The applied hydrophobic membranes allow the passage of water vapor only, while liquid water, suspended and dissolved matter cannot pass. After condensation, theoretically 100 % pure water is obtained. Generally, MD can be operated at ambient pressure and a feed temperature between 50 °C and 80 °C that can be provided by low temperature waste heat, solar thermal energy or geothermal energy. Thus, MD can be considered a low cost, energy saving alternative to distillation and reverse osmosis. There are four basic configurations of membrane modules: direct contact membrane distillation (DCMD), air gap membrane distillation (AGMD), sweeping gas membrane distillation (SGMD), and vacuum membrane distillation (VMD) [25, 26].

Already in 1998, Andres et al. suggested a hybrid process consisting of a multi-effect distiller and the consequent utilization of the heat content of the brines for driving a membrane distillation. This combination was used to improve the performance of pure water production [27]. According to the authors, a production increase of about 7.5 % was detected.

Nellessen et al. conducted MD investigations on pilot scale size with focus on the production of WPU. Commercially available polymeric membranes were used. They conclude that the distillate quality – achieved with AGMD and VDM – complies with the claims of Ph. Eur. for PW in terms of the total bacteria count and the electric conductivity [26]. Maximizing water recovery and minimizing the energy demand, e.g., by internal energy recovery, are still required to optimize of this technology.

According to Woldemariam et al., generally, the specific heat demands for the AGMD range between 692 to 875 $kWh\,m^{-3}$ for systems without heat recovery and ca. 105 $kWh\,m^{-3}$ for systems with heat recovery [28].

An interesting approach seems to be the utilization of ceramic membranes in MD due to their excellent chemical and thermal stabilities, which allow frequent cleaning and sanitization without the risk of membrane damage. However, as conventional ceramic membranes are hydrophilic, they need modification prior to application in MD [29].

Prior to the establishment of MD in the pharmaceutical industry, intensive investigations are required to gain approval of the legislator.

3 Summary

Water is one of the most commonly used sources in the generation of pharmaceutical preparations. High quality demands are placed on water production, distribution, storage, and application. Above all, microbial quality is crucial. As the pharmaceutical industry continues to expand, the importance of sustainable water and energy use becomes crucial to comply with global environmental goals. Pharmaceutical companies can contribute to a greener future by, e.g., leveraging energy-efficient technologies, using renewable energy sources, and promoting sustainability throughout the supply chain.

To establish new resource- and energy-efficient separation technologies, intensive investigations on the long-term behavior are required before approval of the regulatory authorities. Membrane distillation has the potential for applications in purified water production. It can be operated with low temperature waste heat from production lines or with renewable energy sources.

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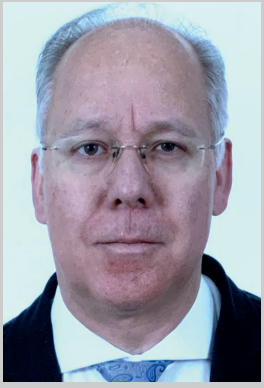

Frank Rögener studied chemical engineering at TU Clausthal, Germany. He received his doctorate in 2000 under the supervision of Horst Chmiel at Saarland University in Saarbrücken on the application of membrane processes in the food industry. Subsequently, he worked as a project leader in the Research and Development Department at Pall SeitzSchenk Filtersystems, Waldstetten, Germany. Afterwards, he worked in different positions and departments at Betriebsforschungsinstitut GmbH (BFI), Düsseldorf, Germany. In 2014, he became Professor of Fluid Process Technology at TH Köln / University of Applied Sciences, Cologne, Germany. Frank Rögener is particularly interested in the development of membrane processes and resource/energy-efficient technologies. He has been guest lecturer at different national and international universities.

Abbreviations

AGMD Air gap membrane distillation
DCMD Direct contact membrane distillation
CFU Colony-forming unit
EDI Electrodeionization
HPW Highly purified water
IX Ion exchange
MD Membrane distillation
ME Multiple effect
Ph. Eur. European Pharmacopeia
PW Purified water
RO Reverse osmosis
SGMD Sweeping gas membrane distillation
TOC Total organic carbon
UF Ultrafiltration
USP United States Pharmacopoeia
VC Vapor compression
VMD Vacuum membrane distillation
WFI Water for injection
WHO World Health Organisation
WPU Water for pharmaceutical use
ZLD Zero liquid discharge

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