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Articles

Calculation of the blue water footprint in the pharmaceutical industry: Case of study for the production process of water for injections

Cálculo de la huella hídrica azul en la industria farmacéutica: caso de estudio para el proceso de producción de agua para inyectables

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Abstract

Society and industry contribute directly and indirectly to the depletion and contamination of water resources. The water footprint is an indicator that measures the total volume of freshwater consumption, and direct or indirect contamination by producers or consumers. The methodology for its evaluation includes three types of footprints: blue, green, and gray. The first two express the volume of water consumed according to the source (aquifers or groundwater for the blue, and rainwater for the green), and the third is the volume contaminated in the production process. This article focused on the calculation of the Water Footprint for the production process of Water for Injections (WFI), in Ecar laboratories in Medellín, Colombia. A comparison is made between the previous conventional distillation system and the new thermocompression system. Additionally, a sensitivity analysis based on the influence of variation of the production efficiency of the new system on the blue water footprint, is presented. As conclusions, it was found that thanks to the reduction of water waste, there was a decrease of 76 % in the water footprint of the new system compared to the previous one. Besides, a higher sensitivity of the water footprint was found when smaller efficiencies of the thermocompression method were considered, evidencing the importance of performing periodical maintenance on the production equipment.

Keywords: Water footprint, pollution, eco-efficiency, water for injections, WFI, pharmaceutical, Colombia.

Resumen

La sociedad y la industria son cada vez más conscientes de que contribuyen directa e indirectamente con el agotamiento y la contaminación del recurso hídrico. La huella hídrica se define como un indicador que mide el volumen total de consumo de agua dulce y la contaminación directa o indirecta por parte de los productores o consumidores. La metodología para su evaluación incluye tres tipos de huellas: azul, verde y gris. Las dos primeras expresan el volumen de agua consumida según la fuente (acuíferos o agua subterránea para la azul, y agua de lluvia para la verde); la tercera indica el volumen contaminado en la producción. Este artículo se centró en el cálculo de la huella hídrica para el proceso de producción de agua para inyectables (API) en laboratorios Ecar de Medellín, Colombia. Se realiza un comparativo entre el sistema anterior de destilación convencional, y el nuevo sistema de termocompresión. Además, se presenta un análisis de sensibilidad basado en la influencia de la variación de la eficiencia productiva del nuevo sistema sobre la huella hídrica azul. Como conclusiones se demostró que gracias a la reducción del desperdicio de agua hay una disminución del 76 % en la huella hídrica del nuevo sistema respecto al anterior. Además, se encontró una mayor sensibilidad de la huella hídrica cuando se consideran menores eficiencias del método de termocompresión, lo que evidencia la importancia de realizar mantenimiento periódico a los equipos de producción.

Palabras clave: huella hídrica, contaminación, ecoeficiencia, agua para inyectables, API, farmacéutica, Colombia.

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Introduction

Water is an essential natural resource for ensuring people's quality of life. Currently, factors such as industrial production, agricultural irrigation and daily domestic activities pose significant challenges to its sustainability over time (Abd-Kadir, Naji, Muhammad, & Bashir, 2024; Çankaya, 2023; Dey, Remesan, & Kumar, 2023; Gosling & Arnell, 2016). This is due to increasing demand and climate changing conditions (Jeyrani, Morid, & Srinivasan, 2021).

Globally, industries represent the second largest consumer of drinking water, with 20 % of all drinking water. This water is used in various industrial processes, including the pharmaceutical sector (Bailey, Basu, & Sharma, 2022), chemical industry (Jungfer & Track, 2016), motor vehicle production (Mueller *et al*., 2015), paper production (Francisco, Mirre, Calixto, Pessoa, & Queiroz, 2014; Manzardo *et al*., 2014), steel production (Colla *et al*., 2017; Gerbens-Leenes, Hoekstra, & Bosman, 2018), textile sector (Raja, Arputharaj, Saxena, & Patil, 2019; Zhou, Xu, Cheng, Xu, & Jia, 2017), as well as the food and beverage industry (Pettigrew, Blomenhofer, Hubert, Groß, & Delgado, 2015; Taylor, Jones, Laing, & Dames, 2018; Valta, Kosanovic, Malamis, Moustakas, & Loizidou, 2015). This is why, due to the limited availability of water resources for the development of industrial activity, it is necessary to implement key strategies to achieve a rational use of this resource (Abd-Kadir *et al*., 2024).

On the other hand, society and industry are increasingly aware that they contribute directly and indirectly to the depletion and contamination of water resources, giving great importance to measures for their integral management (Fridman, Biran, & Kissinger, 2021). As a result, an increasing number of companies have started to calculate their water footprint (WF) and to look for ways to become better water managers (Hoekstra, 2015).

With the rapid development of a circular economy strategy globally and the launch of the national circular economy strategy in Colombia, incentives have been promoted, providing support for research and innovation. Pharmaceutical manufacturers are therefore interested in implementing practical options to close the "water cycle" (Strade, Kalnina, & Kulczycka, 2020).

Most previous studies to quantify the water footprint along the supply chain of specific products have focused on the manufacturing of agricultural and animal products, which are responsible for the largest amount of water consumption in the world (Gerbens-Leenes *et al*., 2018). The industrial sector is the second largest user of water, but product-specific studies are still very scarce (Hoekstra, 2015).

The WF is defined as an indicator that shows the total volume of freshwater consumption, and direct or indirect contamination by producers or consumers. The calculations are made based on the complete supply chain, by tracking the origins of the products. The direct water footprint represents consumption and pollution directly by users, while the indirect one denotes the WF of goods and services used by other people (Hoekstra, Chapagain, Aldaya, & Mekonnen, 2011) and secondary processes.

WF is a parameter that measures the amount of drinking water that is used in industrial processes, or in the daily life of the members of a community, to raise awareness about the amount of water that is wasted and seek sustainability. The volumes of water used can be obtained from

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the government organizations responsible for the availability of the resource.

The calculation methodology includes three types of WF: blue, gray, and green. They express the volume of water consumed or contaminated, however, there are notable differences between them (Hoekstra *et al*., 2011):

Blue WF = Consists of the consumption of fresh surface or underground water. This consumption refers to the loss that occurs when the water evaporates, does not return to the same catchment area, or is returned to the sea, does not return in the same period (is taken in a dry period and returns in a wet one), or is incorporated into a product

Gray WF = Refers to nitrogen pollution and is defined as the volume of fresh water required to assimilate a load of pollutants, given the natural concentrations and environmental standards of water quality, and depending on current environmental legislation

Green WF = refers to the consumption of the water that comes from rains that are not converted into runoff but recharge the groundwater or stays on top of the soil or vegetation. It is incorporated into agricultural products

According to Hoekstra *et al*. (2011), the evaluation of the water footprint is a quantitative tool that can improve the relationship and influence of the different activities and products with the scarcity and contamination of water.

The pharmaceutical industry and its corresponding products are designed to cure people and animals, or to diagnose or prevent diseases (Wöhler, Niebaum, Krol, & Hoekstra, 2020). Water is the most important resource in the pharmaceutical and cosmetics industry, since it is permanently used for the sanitization of the machinery that the process requires. As the products are going to be in contact with living beings, water is subjected to treatment with certain microbiological practices.

In addition, the pharmaceutical industry is one of the most important sectors that extensively uses potable water for the manufacturing of active medicinal substances and finished products such as tablets, capsules, injections, syrups and others. This industry is a highly water-dependent economic sector and requires different degrees of water purity. As a result, there are strict guidelines and standards for the manufacturing of medicines as well as the storage of water in this industry (Abd-Kadir *et al*., 2024; Strade *et al*., 2020).

Due to the above, purified water is used. It is obtained from drinking water, through reverse osmosis (technology that allows the elimination of salinity from water) with techniques such as ultrafiltration and deionization. The former is used to remove dissolved and colloidal materials (Mishra *et al*., 2022), and the latter removes ions, either by exchanging hydrogen ions for cations, or hydroxyl ions for anions (Talat, 2020). Thus, production systems with high biological quality indexes are applied for the manufacture of liquid pharmaceuticals, solid forms, or higher quality products such as injectables.

Another way to obtain drinking water is through double reverse osmosis from purified water, except those that require water quality for injections, which is obtained through the process of distillation of drinking water or reverse osmosis of purified water, which is used for washing sterile mixture equipment and some chemical products. It is necessary to give sufficient importance to the water resource in the pharmaceutical industry, since the quality of the drug depends a lot on it.

Although the studies associated with the calculation of the WF date back to 2002 (Hoekstra, 2017) its application to pharmaceutical products is recent (Wöhler *et al*., 2020). However, there has been extensive research on gray WF related to the use of fertilizers (Liu, Kroeze, Hoekstra, & Gerbens-Leenes, 2012; Mekonnen & Hoekstra, 2015; Mekonnen & Hoekstra, 2018) and pesticides (Gil, Bojacá, & Schrevens, 2017; Lamastra, Suciu, Novelli, & Trevisan, 2014; Vale, Netto, Toríbio-de-Lima Xavier, De-Lâvor-Paes-Barreto, & Siqueira-da-Silva, 2019), but only one case study on the gray WF for human pharmaceutical use has been published (Martínez-Alcalá, Pellicer-Martínez, & Fernández-López, 2018). Additionally, several studies have been carried out to estimate pharmaceutical loads in freshwater (Alder, Schaffner, Majewsky, Klasmeier, & Fenner, 2010; Ter-Laak, van-der-Aa, Houtman, Stoks, & van-Wezel, 2010; Winker, Faika, Gulyas, & Otterpohl, 2008), sewage effluents and in streams (Hirsch, Ternes, Haberer, & Kratz, 1999; Kasprzyk-Hordern, Dinsdale, & Guwy, 2008; Ternes, 1998). Finally, the most recent one has focused on analyzing the loads of human and veterinary pharmaceuticals in water (gray WF) in the context of the assimilative capacity of freshwater systems (Wöhler *et al*., 2020).

The company Ecar Laboratories is situated in Medellin. Due to the demands of the national and international market, they proceeded with the expansion of the installed capacity, the improvement of the quality standards of injectable products, and therefore, the technological renovation. This was accomplished by replacing the conventional distillation system, by a thermocompression one. Thus, they were able to reduce greenhouse gas emissions, the waste of drinking water, and in consequence the WF of the manufacture of injectable products, which led to a reduction in costs in the production of WFI water. Then, the main objective of this article is to develop the calculation of the impact of replacing the conventional distillation system by the thermocompression technology, on the Water Footprint for the WFI water production process. Therefore, the reduction of water waste is expected, in the water footprint of the new system compared to the previous one, corroborating the environmental and economic viability of its implementation. As a complement to the previous one, specific objectives are to measure the sustainability of the water footprint calculation and to analyze the sensitivity on the WF to variations in the production efficiency.

Materials and methods

The evaluation of the WF allows us to quantify the use of water, evaluate its sustainability and identify critical points to be able to reduce it. At the same time, its calculation contributes to the efficient and equitable use of the resource (Pahlow, Snowball, & Fraser, 2015). The water footprint concept is based on the recognition of the influence that human impacts have on freshwater systems. Additionally, it has contributed to the understanding that water scarcity and pollution can be better addressed by considering the manufacturing and supply chains of production processes and service provision (Hoekstra *et al*., 2011).

To assess the water footprint of products and consumers, the Water Footprint Network developed a Water Footprint Assessment methodology to evaluate the impacts on water consumption caused by an activity (Morera, Corominas, Poch, Aldaya, & Comas, 2016). Thus, the calculation of the WF consists of four different phases (Figure 1). First, the objective and scope are established, and the information required for the analysis is specified. In the second phase, an inventory analysis (water footprint accounting) is implemented. In this quantification phase, input/output data is calculated, collected over a specified time, and analyzed to meet the objectives. In the third phase, a sustainability evaluation of the WF is carried out. For the last phase, the response formulation is performed by making the calculation of the reduction in water consumption obtained by replacing the conventional distillation system by the thermocompression one. Below, both systems are described in detail.

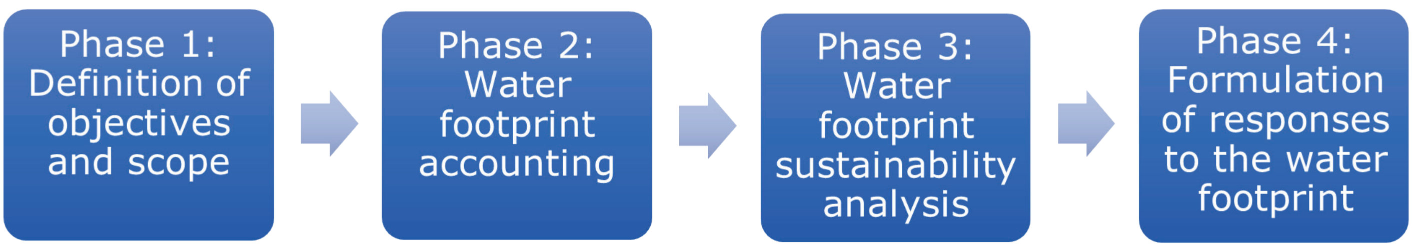

Figure 1. Four different phases of the water footprint assessment. Modified from Hoekstra *et al*. (2011).

By 2018, Ecar had a conventional distillation technology for the manufacture of WFI water that dates back 13 years, which made it productive, economically, and environmentally inefficient. Then, the company made the decision to take a technological leap and started manufacturing WFI water with a thermocompression system. The required initial investment was 408 thousand United States Dollars (USD) in new equipment and around 48 thousand USD in infrastructure adaptations that involved a reengineering of the entire manufacturing process.

Figure 2 presents the flow chart of the conventional distillation process. There is a continuous entry of drinking water that passes through a deionizer, to finally arrive at the conventional distillation system that transforms the water into WFI. It takes five hours to produce 300 liters of WFI water and consumes 25 m^3/h of natural gas. The steam from the boiler enters a steam generator and begins to heat the water, in which the coil is submerged. When the temperature in the steam generator rises, formed water vapor goes up to the condenser or heat exchanger, passing through a special filter that ensures dry, sterile, and pyrogen-free steam. In the exchanger, where there is water cooled by a 10 TR chiller, the thermal shock condenses the steam and the 90 °C distillate passes to the storage tank through valves and sensors that determine the water conductivity and establish whether it is suitable for the process or should be rejected. When distilled water between 25 and 30 °C is required, the 5 TR chiller is put into operation in a smaller exchanger to cool the 90 °C water.

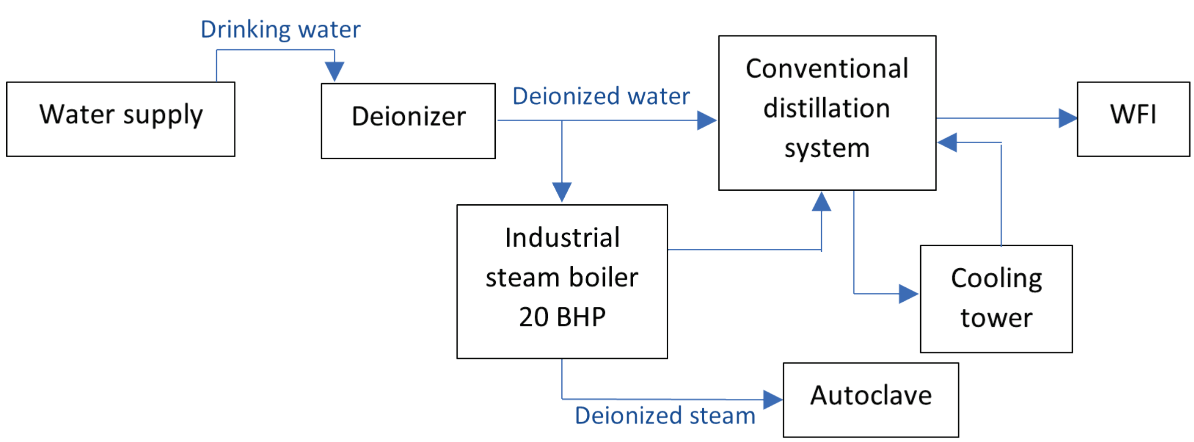

Figure 2. Conventional distillation flow diagram.

Figure 3 shows the new flow diagram to produce WFI water, where the green boxes represent the equipment that was acquired (inversion in

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USD by artifact inside the boxes), and the orange ones the equipment that is currently available or comes from the previous conventional system. The process begins with the supply of drinking water followed by a pretreatment process that seeks to lower the water hardness. The resulting softened water enters the thermocompression distiller that subjects the water to high temperatures and pressures to maximize energy efficiency, thus obtaining WFI water. It is stored in a 1 500 l tank that is constantly kept in motion through a closed loop controlled by a PID, guaranteeing the availability of water all the time, and allowing the generation of WFI steam, a feature that the previous system did not have. The steam improves the quality of sterilization that is carried out today. On the other hand, the natural gas consumption is not modified, and 25 m^3/h are still required.

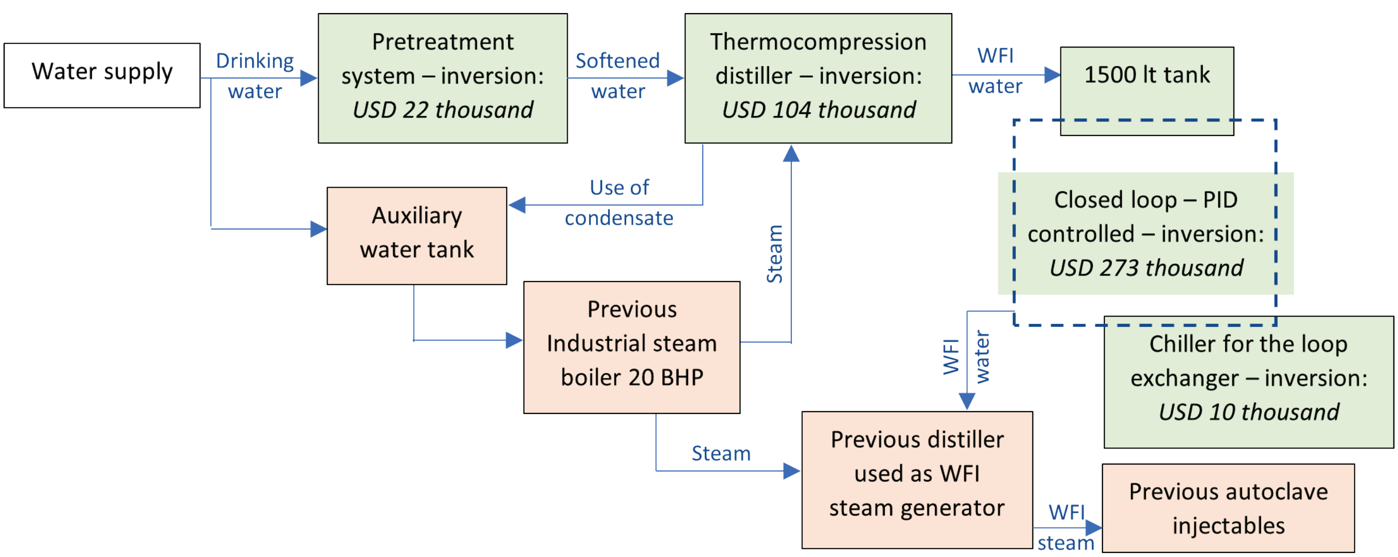

Figure 3. Thermocompression flow diagram.

Next, the methodology of the four phases for the calculation of the WF is described.

Goal and scope

The goal of this study was to determine the impact of direct water consumption on existing water resources for the pharmaceutical industry of WFI. The objective of the analysis was: Evaluate the water footprint reduction due to the Ecar Laboratories conversion of the WFI water generation system by conventional distillation, to a thermocompression generation system, based on the calculation of the blue water footprint.

Water footprint accounting

The general equation to calculate the WF of both systems, which includes the blue (WFblue), green (WFgreen) and gray (WFgray) water footprints, is defined as Equation (1), based on the Hoekstra *et al*. (2011):

$$WF = WFBlue + WFGreen + WFGray \quad (1)$$

Regarding the gray WF, it will not be considered for Ecar Laboratories because the physicochemical parameters with which the water is discharged to the effluent are better than those of drinking water. This can be verified in Table 1, where physicochemical parameters were obtained from different samples that were analyzed based on Colombian regulation for waste water disposal. Then, the wasted or discharged water does not play a polluting role in the receptor body, but a diluting effect on the natural contaminant concentrations that it already has. The calculation of the green water footprint was not considered because this calculation is specifically focused on the analysis of food production, land expansion, irrigation areas, among others (Abd-Kadir *et al*., 2024).

Table 1. Physicochemical parameters of drinking water supply, and of water discharges of Ecar Laboratories systems

System	Parameter	Average
Drinking water	pH	6.74
	Conductivity	31.21 uS/cm
	Total organic carbon	1 300 ppb
Conventional distillation system	pH	6.13
	Conductivity	0.23 uS/cm
	Total organic carbon	58 ppb
Thermocompression distillation System	pH	5.82
	Conductivity	0.45 uS/cm
	Total organic carbon	96 ppb

Drinking water sources include groundwater and surface water, and depending on the context, they are considered suitable for human consumption. Drinking water includes water that has evaporated, water contained in products, water that is not returned to the same catchment area, or water that is not released during the same period (Hoekstra, 2019).

The calculation of the water footprint that is considered pertinent for Ecar corresponds to the blue WF, which is estimated with Equation (2) (Hoekstra *et al*., 2011):

$$\boldsymbol{Blue\ WF = BWIncorp + Wasted\ water} \qquad (2)$$

Where:

$BWIncorp$ = Volume of blue water incorporated to the product manufacture

$Wasted\ water$ = Remaining volume

The latter is calculated with Equation (3):

$$Wasted\ water = BWEvaporation + LostReturnFlow \qquad (3)$$

Where:

$BWEvaporation$ = Volume of blue water evaporated during the manufacture process

$LostReturnFlow$ = Volume of blue water, which is not returned to the same catchment basin, or despite returning to it, it will be available in a different period

The blue WF for Ecar Laboratories will be calculated as volume of water per unit of time for the two systems presented in Figure 1 and Figure 2.

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The blue WF was determined by the water consumption associated only to the previously described systems, not considering other associated volumes such as water consumption by the company operating personnel. For both systems, a fraction of the supplied water was incorporated to the WFI water product ($BWIncorp$), and the remaining one was either evaporated during the manufacture process ($BWEvaporation$) or disposed to the sewerage system. The latter would be combined with wastewater so it would not be available in the same period, becoming $LostReturnFlow$.

Water footprint accounting for the conventional system

To determine the $BWIncorp$ and the $Wasted\ water$ variables for the conventional distillation system, a test of the required time for a total production of 700 l of WFI water was performed three times (Table 2). The $BWIncorp$ was calculated as the ratio of the total production and total time required. A constant potable water supply of 250 l/h was required for each of the tests. Then, $Wasted\ water$ was calculated as the difference between the water supply and $BWIncorp$. The average, sample standard deviation (σ), and the coefficient of variation (CV) were calculated for the required time during the tests, for the WFI water production, and for the wasted water. The effect of the age of the system is evident in the dispersion of the results with respect to the average calculations, with CV values up to approximately 30 %. Variations in time of the system components performance were the cause of this problem.

Table 2. WFI water production test for the conventional distillation system.

Total WFI production (l)	**Total time required (h)**	**WFI production ($BWIncorp$) (l/h)**	$Wasted\ water$ **(l/h)**
700	11	64	186
700	10	70	180
700	17	41	209
Average	**13**	**58**	**192**
σ	**4**	**15**	**15**
$CV(\%)$	**30**	**26**	**8**

The final values used here per unit of time for the conventional system were: 58 l/h for $BWIncorp$, and 192 l/h for $Wasted\ water$.

Water footprint accounting for the thermocompression system

On the other hand, considering the thermocompression system has shown to produce constant WFI water volumes in time, only one hour test was performed (Table 3). Total production during the test was 344.62 l of WFI. A larger constant potable water supply of 350 l/h was required.

Table 3. WFI water production test for the thermocompression system.

Total WFI production (l)	**Total time required (h)**	**WFI production ($BWIncorp$) (l/h)**	$Wasted\ water$ **(l/h)**
344.62	1	344.62	5.38

Water footprint sustainability analysis

The sustainability of the blue WF is defined with Equation (4) (Hoekstra *et al*., 2011):

$$Blue\ WF_{sust} = (\sum Blue\ WF)/(Blue\ WF_{avai}) \quad (4)$$

Where:

$Blue\ WF_{sust}$ = Blue WF sustainability, also known as blue water scarcity in the catchment where the industrial process is located

$\sum Blue\ WF$ = Total of the blue WF in the catchment

$Blue\ WF_{avai}$ = Blue water availability in the catchment

ECAR water supply is provided by Ayurá Water Treatment Plant of Empresas Públicas de Medellín (EPM), located in the southern region of the metropolitan area. This plant has an installed capacity of $9.2\ m^3/s$, then $Blue\ WF_{avai}$ was assumed as $2.9E+11\ lt/year$ (EPM, 2024). It is worth mentioning that the calculation of $Blue\ WF_{sust}$ was performed with the blue WF of ECAR laboratories per year ($Blue\ WF(l/year)$), for the years 2015, 2016, and 2017 in which the company collected data of the total WFI production ($BWIncorp\ (l/year)$) with the conventional distillation system (Table 4).

Table 4. WFI production for the conventional distillation process

YEAR	2015	2016	2017
$BWIncorp\ (l/year)$	29 238	45 914	71 840

$BWincorp\ (l/year)$ data for the thermocompression system is assumed to be the same to compute the reduction in the $Blue\ WF_{sust}$ if during the mentioned period, the company would have had the new system instead of the older one. For the calculation of $Wasted\ water\ (l/year)$, equations (5) and (6) were used:

$$WFI\ time\ (h/year) = \frac{BWIncorp\ (l/year)}{BWIncorp\ (l/h)} \quad (5)$$

$$\boldsymbol{Wasted\ water(l/year) = Wasted\ water\ (l/h) \cdot WFI\ time\ (h/year)} \quad (6)$$

Where:

$WFI\ time\ (h/year)$ = Time in hours for one year, the system requires to produce WFI water

$BWIncorp\ (l/year)$ = Taken from Table 2

$BWIncorp\ (l/h)$ and $Wasted\ water(l/h)$ = Were both taken from Table 3 (average values) and Table 4

Responses for the water footprint and sensitivity analysis

In this phase, the recommended responses to be taken to reduce WF were determined. Then, the considered parameter for a sensitivity analysis was the efficiency of the new Thermocompression system, defined as the ratio of the WFI production ($BWIncorp$), to the volume of required drinking water ($Blue\ WF$) (Equation (7)):

$$efficiency = \frac{BWIncorp}{Blue\ WF} \quad (7)$$

In consequence, alternatively to Equation (2), Blue WF may also be calculated as:

$$Blue\ WF(l/year) = \frac{BWIncorp(l/year)}{efficiency} \quad (8)$$

The selection of this parameter was because the previous conventional system initially required 250 liters of drinking water to produce 200 liters of WFI water, which is equivalent to an efficiency of 80 %. However, due to the age of the equipment its efficiency had fallen to 23 % (250 liters of drinking water to produce 58 liters of WFI water). The influence of decreasing efficiency on the blue WF to achieve the same WFI production obtained in the years 2015, 2016, and 2017, was determined. A range from 90 to 20 % was analyzed.

Results

Water footprint accounting for the conventional and the thermocompression system

For this phase, the quantification of the water consumed in both systems was performed. The calculation of the blue WF was determined by Equation (2). Table 5 presents the blue WF calculation in l/hour.

Table 5. Calculation of water waste for each analyzed system.

Type of system	$BWIncorp\ (l/h)$	$Wasted\ water\ (l/h)$	$Blue\ WF(l/h)$
Conventional distillation flow system	58	192	250
Thermocompression flow system	344.62	5.38	350

Water footprint sustainability analysis

The results of Table 5 do not show the influence that the change of system had on the blue WF. Apparently, the WF of the new system is greater, but this is because it has higher efficiency and production performance per hour. Based on the above, the calculation was performed per year for the data presented in Table 4. The blue WF terms from Equation (2) are shown in Figure 4 for both systems, where $Wasted\ water(l/year)$ was calculated with equations (5) and (6).

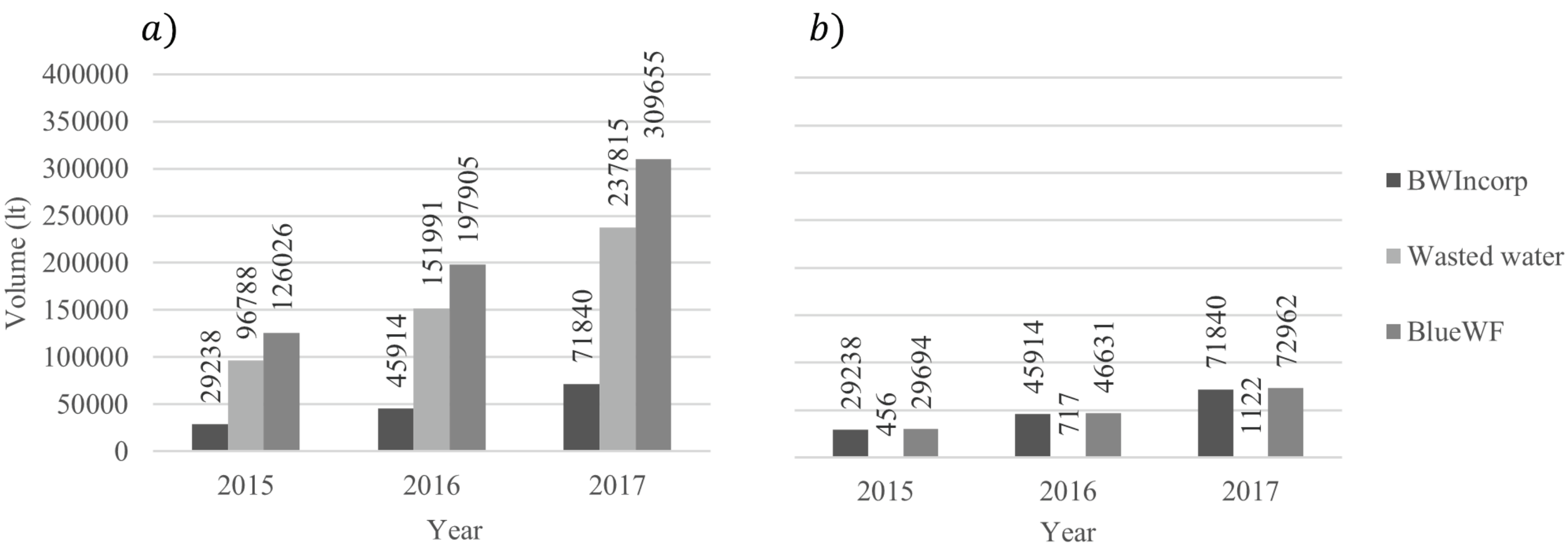

Figure 4. BWIncorp, Wasted water, and BlueWF from 2015 to 2017 for **a)** conventional distillation system, and **b)** thermocompression system.

Blue WF sustainability was calculated with Equation (4) for years 2015, 2016, and 2017 (Figure 5). Then, $\sum Blue\ WF$ was taken from the Blue WF obtained in Figure 4 for each of the systems, and $Blue\ WF_{avai}$ from the installed capacity of Ayurá Water Treatment Plant specified in Methodology section. Additionally, the percentage reduction of blue WF sustainability of the thermocompression system with respect to the conventional one is shown (Equation (9)).

$$Reduction\ (\%) = \frac{Blue\ WF_{sust}\ Conventional - Blue\ WF_{sust}\ Thermocompression}{Blue\ WFsust\ Conventional} \times 100 \qquad (9)$$

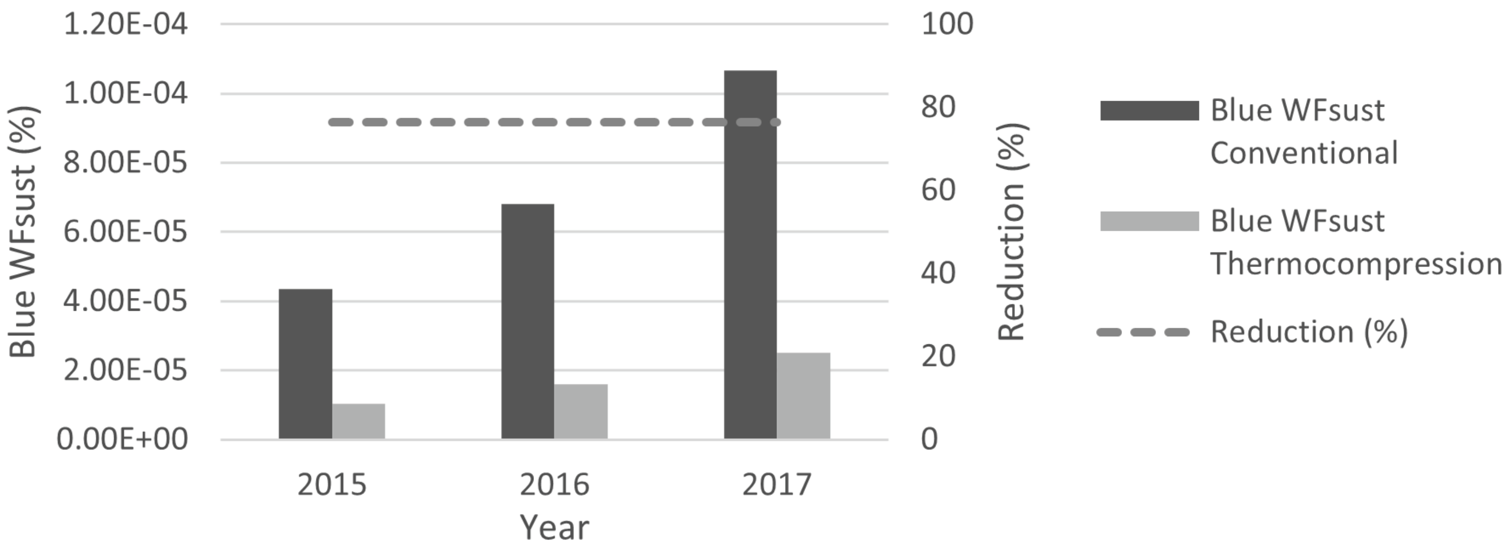

Figure 5. Blue WF sustainability from 2015 to 2017 for conventional distillation system and thermocompression system, with percentage reduction between both systems.

Responses for the water footprint and sensitivity analysis

For responses analysis, the main recommendation from this research is to perform periodic preventive maintenance to the new thermocompression system. This will prevent the efficiency reduction that was evident in the conventional system. Figure 6 presents the sensitivity analysis considering the reduction of efficiency in the range: 90 to 20 %, and its influence on Blue WF generated from the same WFI production obtained in years 2015, 2016, and 2017. Blue WF was calculated as a function of efficiency using Equation (8), with $BWIncorp(l/year)$ from Table 4.

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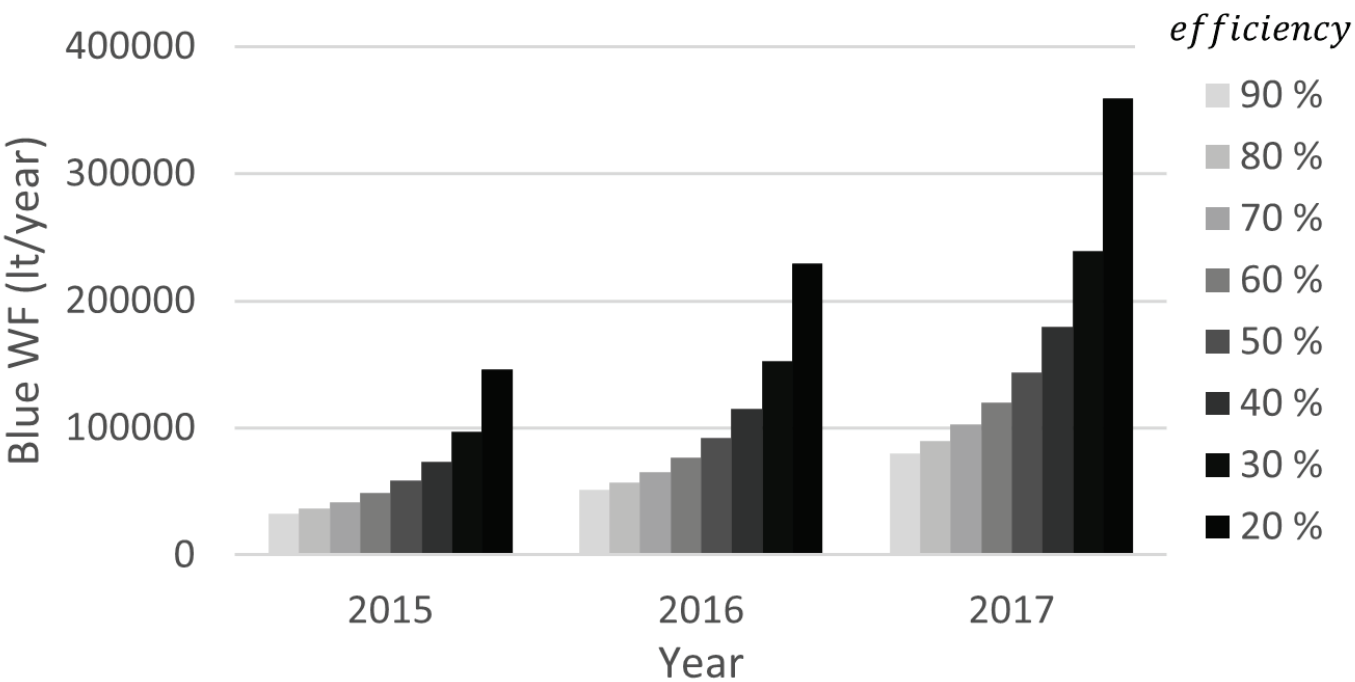

Figure 6. Blue WF sensitivity analysis from 2015 to 2017 for the thermocompression system.

Discussion

Water footprint accounting for the conventional and the thermocompression system

Considering the results obtained with the previous and the current system, a great improvement was made in variables such as efficiency, saving of raw materials, and mainly the production time. The objective of this WF assessment was to identify the relative importance of blue WF, to demonstrate the positive impacts of systems transformation in reducing the environmental impact, and to propose measures to reduce WF in the pharmaceutical industry. Before the modification, there was evidence of a great waste of drinking water in the process, which meant a large percentage of loss, affecting the efficiency, generating cost overruns, and reducing the productivity. With the improvement, the change in the volume of wasted water and the efficiency of the system were evident, increasing the latter up to 98.5 %.

In the pharmaceutical industry, water is an important raw material (Jaimes-Urbina & Vera-Solano, 2020). Likewise, it is used in sanitation processes (Wöhler *et al*., 2020), for washing equipment, packaging, and containers, therefore, generated wastewater is characterized by containing residues of detergents (Martínez-Alcalá *et al*., 2018). Additionally, several studies have shown pharmaceutical loads in freshwater (Alder *et al*., 2010; Ter-Laak *et al*., 2010; Winker *et al*., 2008), sewage effluents, and in streams (Hirsch *et al*., 1999; Kasprzyk-Hordern *et al*., 2008; Ternes, 1998) However, for Ecar, the thermocompression flow system guarantees high quality parameters of the discarded water during its operation (Table 1), and low wasted water (Figure 4b). These results evidence the efficiency in water consumption and its disposal, avoiding discharges of pollutants into the water. WFI is the highest quality water used by the pharmaceutical industry. This is why Ecar Laboratories uses WFI in the manufacture of sterile products and other pharmaceutical products in which endotoxin content must be controlled (Strade *et al*., 2020).

Sustainability assessment of the water footprint

To ensure the sustainability of water resources, the pharmaceutical industry must improve water efficiency in a value chain, as well as maximize opportunities for safe reuse of different grades of water, as proposed by Ecar laboratories in its process of transforming WFI production systems (Strade *et al*., 2020).

Blue WF for the thermocompression system is smaller than for the conventional system, guaranteeing social and economic sustainability. Having a water recirculation process in the new system and avoiding the loss and dumping of contaminated wastewater, ensures that basic human needs are still met for all the habitants of the catchment area (Hoekstra *et al*., 2011; United Nations, 2010).

Blue WF sustainability took $Blue\ WF_{avai}$ from the installed capacity of Ayurá Water treatment plant. The above was considered because the urban water cycle includes the extraction of water from natural resources, the treatment of water to meet the required quality standards and water consumption, as a priority need for the pharmaceutical industry's manufacturing system (Gadipelly *et al*., 2014; Morera *et al*., 2016; Strade *et al*., 2020).

Considering Figure 4 vs. Table 5 results, the time window for the WF calculation should be considered carefully to be able to capture the real effect of the efficiency increase for the new system. The reduction has a great influence on energy consumption and on the cost overruns of Ecar Laboratories. Besides, Figure 4 shows that the wasted water was reduced about 99.5 % each year and the blue WF approximately 76 %, remarking the impact of the efficiency increase. The calculated values of Blue WF for Ecar laboratories show the high volumes of water consumed in WFI production compared to another laboratory engaged in the same process, where around 1 000 l/year were used (Strade *et al*., 2020).

A considerable reduction has been found in the Blue WF sustainability between both systems. Reductions of 76 % for the three years are observed in Figure 5, same as Blue WF reduction discussed in Figure 4. This shows the relevance of the change and the opportunity it represents for an industry that has been characterized by consuming large volumes of water to carry out technological reconversions that bring with them cost-benefit ratios in environmental and economic terms. As the Blue WF sustainability for both systems is below 100 % it can be deduced that they are sustainable production processes.

Responses for the water footprint and sensitivity analysis

Despite the increase of production efficiency of the thermocompression system with respect to the conventional one, both have the same energy consumption: 25 m^3/h of natural gas. In Colombia, the hydrographic areas with the greatest run-of-the-river potential (in the absence of a large dam) have a total potential of 56 187 MW (Unidad de Planeación Minero Energética & Pontificia Universidad Javeriana, 2015). Thus, given the great potential, the implementation of hydrokinetic energies as part of hybrid systems also powered by solar energy and the conventional sources, may contribute to guaranteeing the decrease in usage of fossil fuels.

When comparing this work results with similar ones in literature, no studies with the assessment of the WF for the pharmaceutical industry were found. Then, the WF results for other industries are recalled here. Calculations from Çankaya (2023) for the wastewater treatment sector, conclude that 62 % of the total WF corresponds to the blue WF, while Banerjee, Gautam, Mudliar, Bhaskar y Ghosh (2023) that consider the production of yeast single cell oil, show that this percentage goes down to 14 %. In general, the gray WF plays the major role in the total WF of most industries, however, as was mentioned previously, for WFI production the water is poured into the sewage in better conditions, so blue WF represents 100 % of the total WF. This shows that pharmaceutic WFI sector impact response analysis should focus on the blue WF.

Table 6 presents the comparison of the direct blue WF between the two systems analyzed in the present study, and references considering other sectors of industry, in m^3 of blue water required to produce a single unit of the industry base product. For this work, blue WF to produce 1 m^3 of WFI were derived from the results obtained in Table 5. This research conventional system has a higher consumption of blue water than all the other sectors analyzed. Besides, while the ratio of the blue WF of the conventional system to the blue WF of the other sectors ranges between 1.1 for biodiesel reference to 130.9 for textile reference, the ratio in the thermocompression system ranges between 0.3 to 30.8 for the same references. The reduction of the range limits with the new system is associated to the increase of efficiency, and it shows the importance of considering a sensitivity analysis of the influence of this factor on the resulting blue WF.

Table 6. Comparison of the direct blue WF (in m^3 of water per unit of base product) between the present study and other industries considered in the state of the art.

Industry	Reference	Unit of base product	Direct blue WF (m^3)
Pharmaceutic - WFI	Present study: Conventional	1 m^3 of WFI	4.310
	Present study: Thermocompression	1 m^3 of WFI	1.016
Wastewater treatment	Çankaya (2023)	1 m^3 of treated wastewater	0.441
Wastewater treatment	Morera *et al*. (2016)	1 m^3 of treated wastewater	0.055
Biodiesel production	Banerjee *et al*. (2023)	1 kg of yeast single cell oil	3.820
Textile manufacture	Luo, Wu, and Ding (2022)	1 pair of jeans	0.033

Results plotted in Figure 6 show an inverse proportionality of the analyzed variables, in which the lower the efficiency, the larger the blue WF. However, there are two important aspects to highlight. First, a nonlinear relation is observed since uniform decrements of efficiency (10 %), produce higher increments of blue WF as efficiency approaches 20 %. Furthermore, year 2017 with the highest $BWIncorp\ (l/year)$ (Table 4) depicts the largest blue WF increments with decreasing efficiency. The former aspect shows a higher sensitivity of the WF to smaller efficiencies in the production process, and the latter shows more sensitivity to years of larger production of WFI. To prevent the thermocompression system from reaching conditions of high sensitivity, it is indispensable to perform periodic preventive maintenance.

Conclusions

Considering that the present study's main objective was to develop the calculation of the impact of replacing the conventional distillation system by the thermocompression technology, on the Water Footprint for the WFI water production process, the following conclusions were achieved in terms of all the stages considered in WF methodology.

To evidence the effect of increasing efficiency of the thermocompression system on the Blue WF reduction, it was important to consider a time window large enough to visualize the influence of the production time decrease on the reduction of the total volume required to manufacture a given amount of WFI. For Ecar laboratories a time window of one year was required.

The technological advance of replacing the conventional system by the thermocompression one resulted in a reduction of wasted water of about 99.5 % per year, and a Blue WF and Blue WF sustainability reduction of approximately 76 % per year. It showed the high sensitivity of production processes to the system efficiency.

Finally, it was found that the lower the efficiency, the larger the Blue WF. Besides, the efficiency sensitivity analysis highlighted a higher sensitivity of the Blue WF to smaller efficiencies in the production process, and more sensitivity to years of larger production of WFI. This evidenced the importance of maintaining stable efficiency of the system over time, and of performing periodical maintenance on the production equipment.

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