



Development and testing of a nanobubble-based hydrodynamic cavitation system

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ABSTRACT

Emerging pollutants pose a significant challenge to conventional water and wastewater treatment technologies, highlighting the need for targeted and energy-efficient advanced oxidation processes. Although hydrodynamic cavitation (HC) has shown promising results, the potential of nanobubble-assisted HC remains largely unexplored. In this study, a specialized Venturi tube designed for nanobubble generation was developed and implemented in a pilot-scale (14 L) HC system for the degradation of humic acid (HA) and five active pharmaceutical ingredients (APIs) (climazole, sulfadiazine, sulfamethazine, sulfapyridine, and venlafaxine).

A response surface methodology (RSM) framework was applied to optimize the Venturi geometry, resulting in a high nanobubble fraction (ca. 90% < 1 μm), with a mean diameter of approximately 151 nm and a zeta potential of -15.4 mV. To further explore the design space, neural network modelling based on 10 prototypes was employed. The analysis revealed that reducing the throat diameter (D_t) to 0.5 mm could decrease the mean bubble diameter to approximately 90 nm, but with a four-fold reduction in hydraulic throughput (20 vs. 80 L/h), highlighting a critical trade-off between bubble size minimization and treatment capacity.

In degradation tests, sodium persulfate (PS) consistently outperformed hydrogen peroxide (H_2O_2) as an auxiliary oxidant. PS-assisted HC achieved ca. 56–88% primary degradation of the tested APIs and ca. 60% mineralization for HA. This performance was governed via rapid oxidant activation within the first 5–15 min, followed by sustained hydroxyl radical generation driven by hydrodynamic cavitation.

Notably, the system operated without external energy inputs such as UV irradiation or ultrasonic transducers. Consequently, nanobubble-assisted HC represents a scalable, reagent- and energy- efficient water and wastewater treatment process, capable of delivering performance comparable to more complex hybrid processes.

1. Introduction

Water covers over 75% of the earth's surface; however, only a small portion is fit for human consumption. Of all the water on Earth, just 2.5% is freshwater, while the remaining 97.5% is saline. Moreover, approximately 69% of freshwater is locked in polar glaciers, and about 30% exists as groundwater, which is often difficult and costly to extract [1,2].

Only about 1.2% of freshwater is available as surface water, making it the most accessible source. Yet even this limited supply is increasingly threatened by contamination. Safeguarding drinking water quality is therefore critical, as it is directly linked to human health; exposure to

chemical pollutants can lead to both short- and long-term health effects [3–5].

In recent years, a wide range of emerging contaminants, including active pharmaceutical ingredients (APIs), have been increasingly detected in water resources at different concentrations, (e.g., sulfadiazine (SLD) (34 ng/L) and climazole (CLI) (1100 ng/L)) [6]. These compounds comprise multiple pharmaceutical classes, from antibiotics to antifungals. While certain APIs (e.g., ibuprofen and naproxen) are effectively removed during conventional biodegradation, many others exhibit higher persistence. These recalcitrant compounds often bypass standard wastewater treatment processes, leading to their continued presence in the aquatic environment [7,8].

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Several studies have shown that APIs residues can disrupt key microbial functions in aquatic ecosystems, such as nitrite oxidation and methanogenesis or contribute to the proliferation of antibiotic-resistant bacteria. For example, azithromycin has been shown to inhibit nitrifying bacteria and promote the enrichment of resistance genes [9]. Beyond microbial impacts, exposure to psychotropic APIs such as venlafaxine (VEN) has been linked to histopathological damage in fish liver and kidneys, as well as to endocrine disruption, including feminization in male specimens [10,11].

For these reasons, removing APIs from water and wastewater is fundamental for both environmental and human health protection, requiring the development and implementation of suitable treatment technologies. Among the most effective methods are advanced oxidation processes (AOPs), which rely on the generation of highly reactive radicals, such as hydroxyl radicals ($\text{OH}^\bullet$) and sulfate radicals ($\text{SO}_4^{\bullet-}$), to oxidize the target contaminants [12]. In detail, hydroxyl and sulfate radicals can be produced through various AOP techniques, following the reaction mechanisms outlined in Eq. 1-Eq. 5 [13,14].



However, the efficiency of AOPs is significantly influenced by the complexity of the treated matrix. In detail, various water and wastewater components, such as salts and organic matter, can interfere with the treatment by i) scavenging oxidating species thereby increasing oxidant demand and reducing process efficiency [15], ii) blocking active adsorption sites, iii) promoting membrane fouling causing flux decrease, more frequent cleaning cycles, and higher replacement costs [16], iv) leading to the formation of unwanted byproducts, and iv) inducing emulsification phenomena [17,18]. In fact, a particularly challenging component is humic acid (HA), which poses several obstacles in both water and wastewater treatment [12,19], as it acts as i) the scavenger for reactive oxidative species, ii) precursor for disinfection by-products (DBPs) [20], iii) accumulates on membrane surfaces and iv) increases coagulant demand and sludge production [21].

For these reasons, in order to mitigate these issues, it is essential to remove or reduce HA prior to the application of AOPs. This necessitates the development and integration of innovative cost-effective and sustainable pre-treatment technologies.

In this context, hydrodynamic cavitation (HC) has emerged as a promising AOP with increasing attention over the past two decades [22]. In detail, HC has been shown to operate with relatively simple set-up and operational costs, requires less chemicals and energy than other technologies with similar performances (e.g., UV/ H_2O_2 , Fenton and photo-Fenton process) [23–25], and can be effectively integrated into existing treatment trains as a pre-treatment step to enhance overall system performance [26,27].

In detail, HC is a process used to produce cavitation bubbles in a flowing liquid using pressure variations, usually achieved through Venturi tubes, orifice plates, or rotating cavitation generators [28]. Such processes are governed by Bernoulli's equation (i.e., Eq. 6), where the liquid's pressure drops as the pipe's diameter is reduced, inducing cavitation and the formation of both micro- and nano- bubbles. Their collapse leads to very high localized temperatures (up to ca. 7200 K) and pressures (up to ca. 10^8 Pascal), enabling hydroxyl radical formation [29,30].

$$P + \frac{1}{2}\rho U^2 = C(\text{constant}) \quad (6)$$

Where U is the flow rate of the liquid at a certain point, P is the pressure, and ρ is the density of the liquid.

Several studies have shown promising results in using nanobubble-based HC for the degradation of organic chemicals due to the increased surface-to-area ratio of nanobubbles, and their longer half-life with respect to micro-bubbles [31,32]. However, only few studies have explored the application of nanobubble-based cavitation systems specifically for the treatment of water and wastewater, especially at pilot- or full-scale. In fact, existing studies have been typically restricted to laboratory-scale or very low volumes (i.e. from 100 mL to 2 L), thus limiting their representation of full-scale treatment systems [33–36].

Among the various processes applied to induce cavitation, several works have shown that the use of Venturi tubes favours the formation of nanobubbles and that the configuration of the Venturi can greatly influence the nanobubbles' characteristics [37–41]. In detail, these systems were studied by characterising the produced bubbles considering i) the fraction of nanobubbles (%) (i.e., volumetric fraction of bubbles with hydrodynamic diameter below 1 μm , hereinafter referred to as frequency) [42], their average hydrodynamic diameter (nm) and ii) their average Z-potential (mV) (i.e., overall average surface charge of the bubbles). In detail, hydrodynamic diameter is related to both the surface-to-area ratio and rising velocity of the bubbles, thus influencing their diffusion in the water. Bubbles' surface charge (measured as Z-potential), through electrostatic repulsion phenomena, controls their tendency to coalesce and prevents them from exploding as it counters Laplace pressure-driven dissolution (Eq. 7).

$$\Delta P = 2\gamma/R \quad (7)$$

where ΔP is the pressure difference between the inside and outside of the bubble, γ is the surface tension and R is the radius of the bubble.

In this study, the development of a pilot-scale (i.e., 14 L of treated water) Venturi-based HC system favouring the formation of nanobubbles with negative Z-potential was carried out, and its performance was investigated for the degradation of HA and five APIs (i.e., CLI, SLD, SLM, SLP, and VEN) covering different pharmaceutical classes (i.e., antifungals, antibiotics, and antidepressants) previously shown to be responsive to cavitation-based degradation [43–47].

In detail: i) a preliminary screening of Venturi tube configurations was conducted based on literature data to identify designs that enhance nanobubble properties (i.e., high bubble frequency, small average diameter, and negative Z-potential); ii) ten configurations were then selected using a Design of Experiments (DoE) and Response Surface Methodology (RSM) approach, and a Teflon prototype was built for each; iii) the bubbles produced by each prototype were characterized in terms of frequency, average hydrodynamic diameter, and Z-potential; iv) a stainless-steel Venturi tube was fabricated based on the configuration that generated the highest number of nanobubbles with low Z-potential; v) a pilot-scale HC system was subsequently developed using the optimized Venturi design, and its performance was evaluated for the degradation of HA and five APIs, both in the presence and absence of additional oxidants (hydrogen peroxide, sodium persulfate), and vi) finally, to further investigate Venturi designs that could not be physically constructed due to technical limitations, the experimental results from the ten prototypes were used to develop, train, and validate a neural network model capable of predicting bubbles' hydrodynamic diameter, frequency and surface charge (Z-potential).

2. Materials and methods

2.1. Chemicals and reagents

Humic acid (HA, technical grade, Fluka Chemika) was used as a

proxy for NOM (Fig. 1) and dissolved in MilliQ water to prepare a 200 mg_{TOC}/L stock solution. In detail, the NOM stock solution was prepared by adding 344.7 mg of HA to 250 mL of MilliQ water, stirred in the dark at room temperature for 36 h and centrifuged 3 times at 9000 rpm for 15 min using a centrifuge (Eppendorf 5910Ri) to eliminate any suspended particles.

Sodium persulfate (Na₂S₂O₈, ≥ 98%, Merck) and hydrogen peroxide (H₂O₂, 30% w/w, Merck) were used as oxidizing agents. A 1.37 M sulfuric acid solution (H₂SO₄, 98% w/w, Merck) was used for pH adjustment during HC experiments. A 45 g/L solution of sodium sulfite (Na₂SO₃, ≥98%, Carlo Erba) in MilliQ water was used as radical quenching agent to avoid further reaction of the oxidants used in the cavitation experiments, with a Na₂SO₃:oxidant molar ratio of 22 for PS and of 195 for H₂O₂ [48–50]. Climbazole (CLI), sulfadiazine (SLD), sulfamethazine (SLM), sulphapyridine (SLP), and venlafaxine (VEN) (Fig. 1), used for HC testing (≥ 98% purity) were procured from Merk (Darmstadt, Germany), while internal standards for LC-MS analysis (≥ 95% purity) were acquired from LGC standard (Middlesex, UK).

2.2. Instrumental analysis

2.2.1. Total organic carbon (TOC) analysis

The concentration of Total Organic Carbon (TOC) in the water samples was measured in triplicate analysis using a Shimadzu TOC-5000 analyzer. The system utilizes 680 °C catalytic combustion and non-dispersive infrared (NDIR) detection to determine both total carbon (TC) and inorganic carbon (IC) [65]. The relative standard deviation for all TOC measurements was below 5%; therefore, error bars are omitted from the figures. Specifically, TOC was monitored only for HA, as the individual APIs were present in a multi-component mixture at concentrations near the instrumental detection limit (ca. 0.1 mg-C/L). This concentration was insufficient to reliably quantify mineralization or

attribute TOC changes to specific parent compounds.

2.2.2. LC-MS/MS for API analysis

Concentration of the selected APIs in water samples were measured in triplicate using a UHPLC system (Waters ACQUITY Premier) equipped with a BEH C18 column (2.1 × 50 mm, 1.7 μm) maintained at 35 °C, coupled with a triple quadrupole mass spectrometer (Waters Xevo TQ Absolute) equipped with an electrospray ionization (ESI) source operating in both positive (+ESI) and negative (−ESI) modes. Water samples were centrifuged at 9000 rpm for 15 min prior to analysis, and 10 μL of internal standard solution was added to 300 μL of the prepared sample. The analysis was carried out via direct injection, using a mobile phase composed by the following components: A) UPW + 0.01% formic acid and B) ACN +0.01% formic acid (See Supplementary Information S1 (method description and validation), for additional information). The parameters of the ESI source were set as reported in Table S3. Additionally, the selected APIs were analysed in MRM mode, with specific transitions optimized for each analyte and internal standard (IS). Collision voltages (CV) and collision energies (CE) were individually optimized to ensure optimal sensitivity and selectivity. The complete list of transitions is reported in Table S4. Furthermore, the developed method was validated in terms of specificity, precision, accuracy, MDL, and MQL (for detailed model description and validation methods see Section S1 of the Supplementary Information).

2.2.3. Electrophoretic light scattering

Surface charge of the electric double layer of the bubbles produced by the tested Venturi tubes was investigated by means of Electrophoretic Light Scattering (ELS) analysis (HORIBA - SZ100, HORIBA Ltd., Japan) by applying a 5 V electric field to obtain Z-potential values. In detail, 4 mL samples were taken every 5 min directly from the cavitation tank after the HC device ran for a pre-equilibration period of ca. 10 min. Ten

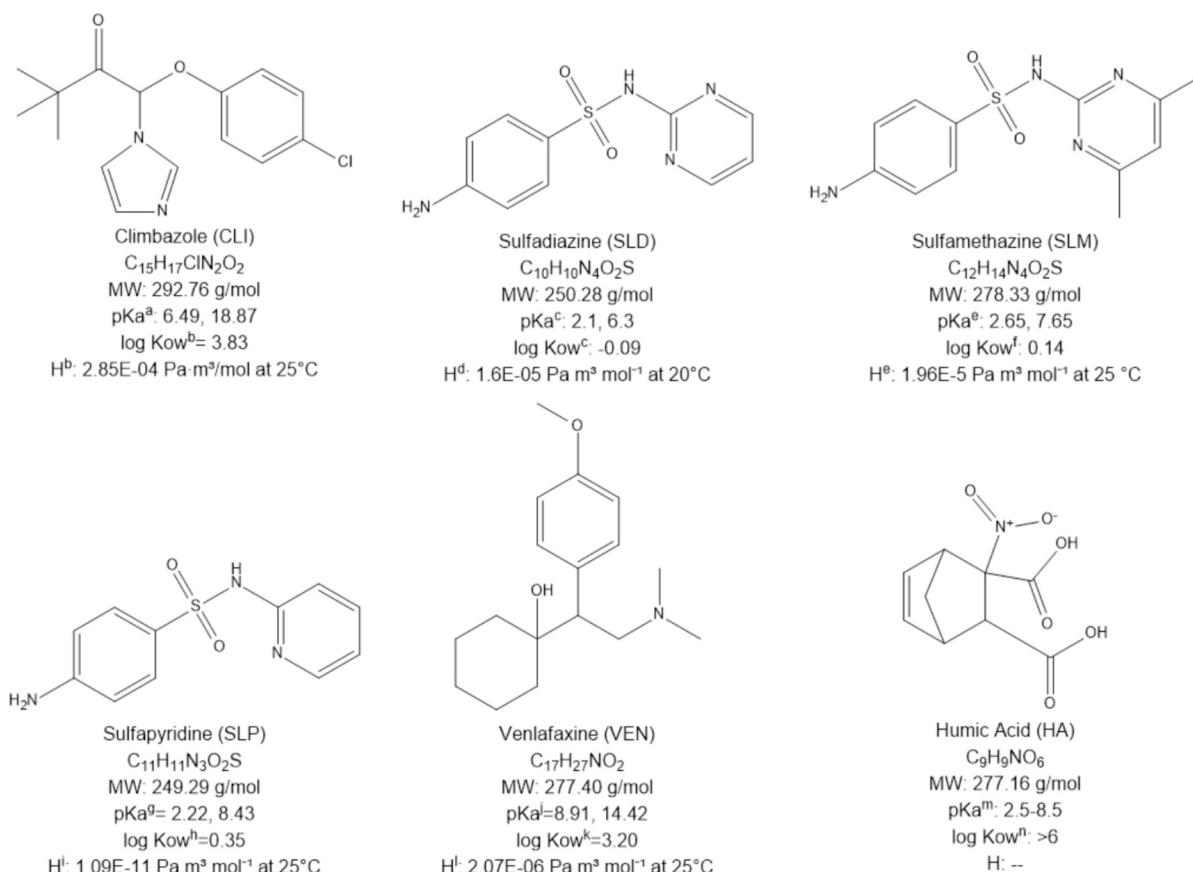


Fig. 1. Chemicals selected for this study. ^a: [51], ^b: [52], ^c: [53], ^d: [54], ^e: [55], ^f: [56], ^g: [57], ^h: [58], ⁱ: [59], ^j: [60], ^k: [61], ^l: [62], ^m: [63], ⁿ: [64].

samples were taken for each prototype to ensure reproducibility and accuracy of the results [66,67] (See Section 2.3.1 for additional details on the HC system used for prototype testing).

2.2.4. Laser particle size analysis

Hydrodynamic diameter and volumetric distribution (volumetric fraction of bubbles with hydrodynamic diameter below 1 μm , will be referred to as “nanobubbles frequency”) of the bubbles produced by the tested Venturi tubes were measured using an in-line Malvern Mastersizer 2000 (Malvern Panalytical, Malvern, UK) laser particle size analyzer (LPSA). In detail, measurements were carried out using an optical fibre sensor ($W = 25 \text{ mW}$ and $\lambda = 639 \text{ nm}$) set at 90° to the water flow [38,68] (See Section 2.3.1 for additional details on the HC system used for prototype testing).

2.2.5. pH

pH of treated and untreated water samples was measured using the APAT-CNR-IRSA 2060 method [69].

2.3. Experimental

2.3.1. Venturi tube design and prototype testing for nanobubble production

In order to develop a Venturi tube able to favour the formation of nanobubbles with both small hydrodynamic diameter and most negative surface charge (i.e., negative values of Z-potential), previous works were reviewed to determine which design parameters influenced the production of bubbles the most. In detail, information from Deng et al., (2020), Pourkarimi et al., (2017), and Xiong and Peng, (2015) was used to define the range of values considered in this work for throat diameter (D_t , from 0.5 to 2.5 mm), connection length (L_1 , from 12.7 to 14.15 mm), convergence length (L_2 , from 67.15 to 72.85 mm), and convergence angle (α , from 1.96 to 2.22°) (Fig. 2).

Consequently, to maximize coverage of the design space and select the most significant configurations to be built and tested a Design of Experiment (DoE) approach was used by applying Response Surface Methodology (RSM) [70]. The DoE process was conducted using Design Expert software (Version 13) with a full factorial design to ensure comprehensive exploration of parameter combinations, resulting in 24 initial designs (Table 1).

The 24 proposed designs were further evaluated based on a literature review and technical limitations associated with available drilling instruments. Specifically, i) design 4 ($D = 0.5 \text{ mm}$) was excluded due to the unavailability of suitable laser drilling equipment and the high risk of mechanical drill breakage during production and ii) design 16 ($D = 2.5 \text{ mm}$) was excluded based on literature findings indicating suboptimal performance with regards to nanobubble production [38,71]. Moreover, based on the results reported by Wang and Wang (2023) and English (2024) [72,73], four designs with $D_t = 1 \text{ mm}$ (Design 6, 12, 20, and 22), four with $D_t = 1.5 \text{ mm}$ (Design 3, 18, 21, and 24), and 2 with $D_t = 2 \text{ mm}$ (Design 5, and 7) were selected for further study.

Furthermore, it should be noted that the design developed in this work (Fig. 2) features a converging section followed by a straight exit (i.e., a divergence angle of 0°), which discharges directly into the cavitation tank. This geometry aligns with the principles described by

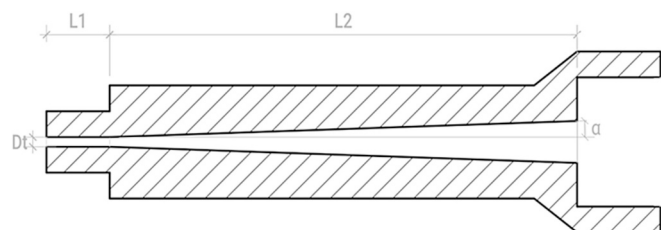


Fig. 2. Venturi tube general design parameters: i) throat diameter (D_t), ii) throat length (L_1), iii) convergence length (L_2), and iv) convergence angle (α).

Table 1

Venturi tube designs considered in this work. Designs highlighted in bold were selected for prototype testing.

Design	D_t (mm)	L_1 (mm)	L_2 (mm)	α (°)
1	1.00	9.85	72.85	2.14
2	1.50	7.00	75.70	2.05
3	1.50	7.00	70.00	2.22
4	0.50	7.00	70.00	2.05
5	2.00	9.85	72.85	2.14
6	1.00	9.85	72.85	1.96
7	2.00	4.15	67.15	1.96
8	1.50	7.00	70.00	1.88
9	1.00	4.15	67.15	1.96
10	2.00	4.15	72.85	2.14
11	2.00	4.15	72.85	1.96
12	1.00	4.15	72.85	1.96
13	2.00	9.85	67.15	2.14
14	2.00	4.15	67.15	2.14
15	1.00	4.15	72.85	2.14
16	2.50	7.00	70.00	2.05
17	2.00	9.85	67.15	1.96
18	1.50	7.00	64.30	2.05
19	2.00	9.85	72.85	1.96
20	1.00	4.15	67.15	2.14
21	1.50	4.15	70.00	2.05
22	1.00	9.85	67.15	2.14
23	1.00	9.85	67.15	1.96
24	1.50	12.70	70.00	2.05

Pourkarimi et al. (2018) [74], who suggested that this configuration favours the generation of nanobubbles.

Finally, a prototype for each selected design was built using polytetrafluoroethylene (PTFE) due to its chemical, thermic, and structural stability.

2.3.2. Hydrodynamic cavitation systems set-up

Two separate cavitation systems were built for the purpose of prototype selection (i.e., system 1) and degradation efficiency evaluation (i.e., system 2) using configuration shown in Fig. 3. In detail, both systems used: i) a closed-loop circuit for cavitation equipped with a heat exchanger located between the pump and the Venturi tube in order to prevent the temperature from rising above 40°C [75], ii) a bypass installed before the Venturi tube to regulate water flow and pressure in the system [24], iii) a no return valve to prevent backflow into the tank, and iv) an air valve positioned before the pump to release air from the system during filling operations.

System 1 (prototype testing) used the following components: i) a centrifugal pump (i.e., 1.1 kW, 4 bar, 50 m and 5000 L/h), ii) a tank with a volume of 8 L, iii) a T junction used to bring a flow of about 500 L/h to the on-line LPSA, iv) an immersion helical-coil heat exchanger in 316 L stainless steel with 10 spirals (total length of ca. 157 cm) submerged in a tank filled with cooling water (70 L, $15\text{--}20^\circ\text{C}$, 22 L/h) keeping the temperature at $35 \pm 2^\circ\text{C}$, and v) each run lasted 60 min to ensure equilibrium, and each prototype was tested three times.

System 2 (degradation testing) used the following components: i) a pump (i.e., 1.3 kW, 5.5 bar, 55 m, 6000 L/h), ii) a tank with a volume of 20 L, iii) a heat exchanger comprising 7 spirals of plastic pipes in PVC (total length of ca. 176 cm), submerged in a tank filled with cooling water (100 L, $15\text{--}20^\circ\text{C}$, 27.5 L/h) keeping the temperature below 36°C .

Both systems were operated at a pressure of 4 bar at the inlet of the Venturi tube, resulting in water flow rates of approximately 20–150 L/h, depending on the throat diameter of the tested Venturi tube. When an additional oxidant was used, the appropriate solution was added directly into the tank immediately after the system reached the operating pressure of 4 bar. Before and after each experiment, the HC system was flushed with deionized water for 15 min at 3 bar to ensure proper cleaning.

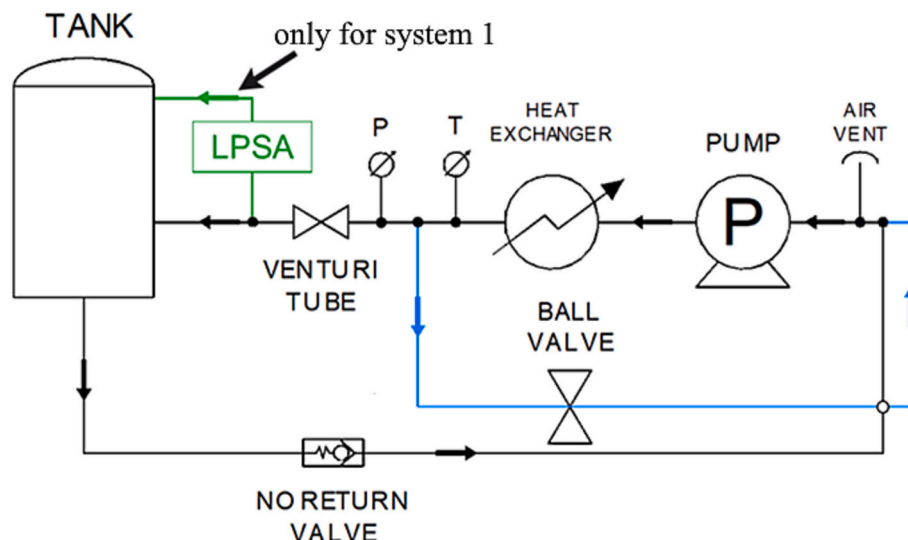


Fig. 3. Schematic of the HC systems used to investigate the performance of the selected Venturi tube prototypes for nanobubbles production (system 1) and the performance of the final Venturi tube design in degrading the selected chemicals (system 2). The black line indicates the hydrodynamic cavitation loop. The blue line indicates the bypass between the pump and the Venturi tube used to modulate system pressure and water flow. The green line indicates bypass through LPSA used only during the prototype testing process in system 1.

2.3.3. Neural network modelling of Venturi tube specifics and nanobubble characteristics

As previously discussed, several studies have explored the influence of Venturi geometry on nanobubble generation [38,76,77]. In fact, minor geometric changes, such as in convergence angle (α) or throat diameter (D_t) can significantly affect bubbles' characteristics [78]. However, the number of prototypes to be built and tested had to be limited due to manufacturing and budget constraints, therefore the DoE approach may not have adequately captured the full design space, potentially overlooking superior designs. In detail, while RSM is effective for identifying dominant main effects and low-order interactions within a predefined experimental domain, it is inherently limited by its polynomial structure and by the assumption of smooth, low-order relationships between variables. In contrast, ANNs do not impose a predefined functional form to the input–output relationship and are therefore able to capture highly nonlinear, coupled interactions among geometric parameters that may remain hidden to RSM, particularly when interaction effects vary locally across the design space [79,80].

In the present study, the use of an ANN model enabled exploration of geometric configurations beyond those directly accessible by the DoE, including parameter combinations associated with impractical or non-standard manufacturability. This capability allowed the identification of coupled and interdependent effects of geometric parameters among throat diameter, convergence angle, and connection lengths (i.e., L_1 and L_2) that could not be resolved through the response surfaces obtained from RSM alone [79,80].

For this reason, an ANN model was developed, following established strategies for small-dataset regression problems, where model size and training is intentionally restricted to improve generalization and prevent overfitting [81]. In fact, prior studies have shown that shallow feed-forward neural network with a limited number of hidden neurons can outperform deeper architectures under data-scarce conditions by reducing variance and preventing memorization of experimental noise [81–83]. Accordingly, compact architecture was selected, and training complexity was further controlled by limiting the number of training epochs.

In detail, the ANN model was developed with 4 inputs (i.e., throat diameter (D_t), first length L_1 , second length L_2 , and convergence angle (α)), and 3 outputs (i.e., diameter of the bubbles, frequency of the nanobubbles, and Z-potential).

Due to the small number of experiments, in order to prevent over-

fitting, the size of hidden layers of the neural network was set at 3, the number of epochs was set at 10, and the weight regularization factor was set to 0.2 [84]. Similar to what has been already reported for small datasets, no data was used for validation, but only for training (60%) and testing (40%) [85].

The selected neural network was a feed-forward neural network composed of “trainlm” as the training function, “tansig” as the activation function in the hidden layers, and “purelin” in the output layer. The weights and biases for both the hidden and output layers are shown in Table 2, while, the network architecture and characteristics are shown in Fig. 4 and Table 3, respectively.

The model was executed using all possible combinations of design parameters, with each range discretized into 20 intervals. This discretization was selected by iteratively running the model with increasing numbers of intervals (i.e., 5, 8, 10, 15, 20, 30, 50, 80, and 100) and then choosing the smallest interval count beyond which no statistically significant differences in the results were observed according to Pawluk-Kotc et al. (2006) and Pianosi et al. (2016) [86,87].

Finally, to evaluate the performance changes of each modelled design relative to the best configuration identified by the DoE approach, a scoring system was developed. The characteristics of the nanobubbles produced by the final prototype ($D_t = 151.7$ nm, frequency = 89.65%, and Z-potential = -15.4 mV) were used as the benchmark (Eq. 8 - Eq. 11). In detail, higher scores were assigned to designs yielding a smaller hydrodynamic diameter, a higher frequency, and a higher absolute Z-potential compared to the benchmark.

$$D_{score} = \frac{(D_{benchmark} - D_i)}{D_{benchmark}} \cdot W_D \quad (8)$$

$$F_{score} = \frac{(F_i - F_{benchmark})}{F_{benchmark}} \cdot W_F \quad (9)$$

$$Z_{score} = \frac{(\text{abs}(Z_i) - \text{abs}(Z_{benchmark}))}{\text{abs}(Z_{benchmark})} \cdot W_Z \quad (10)$$

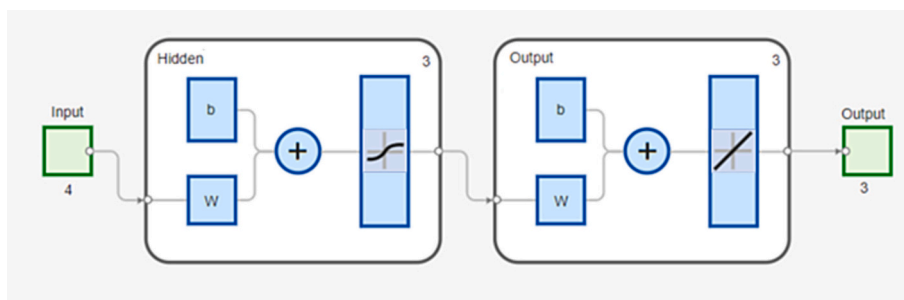
$$Tot_{score} = D_{score} + F_{score} + Z_{score} \quad (11)$$

where D is hydrodynamic diameter, F is frequency, Z is Z-potential, and $W_{D/F/Z}$ are weight representing the importance of each parameter. The weights of the scoring system ($W_D = 0.4$, $W_F = 0.2$, $W_Z = 0.4$) were selected based on the fact that during water treatment, hydrodynamic

Table 2

Weight and biases for hidden layers and output layers of the neural network.

Weights connecting inputs to the hidden layer (W_1)	Biases for the hidden layer (b_1)	Weights connecting the hidden layer to the output layer (W_2)	Biases for the output layer (b_2)
$\begin{bmatrix} 0.16437 & -0.1646 & -0.3551 & -0.0708 \\ 0.7593 & 0.7047 & -0.1623 & 0.1295 \\ -0.4335 & 0.2571 & 0.4243 & -0.0675 \end{bmatrix}$	$\begin{bmatrix} 0.0646 \\ -0.0172 \\ -0.3035 \end{bmatrix}$	$\begin{bmatrix} 0.1570 & 0.4811 & -0.4871 \\ -0.2670 & -0.2104 & 0.7332 \\ -0.0663 & -0.8643 & 0.0698 \end{bmatrix}$	$\begin{bmatrix} -0.0403 \\ -0.0478 \\ 0.0496 \end{bmatrix}$

**Fig. 4.** Neural network architecture: inputs, hidden layers, transfer functions, and outputs.**Table 3**

Neural network architecture of hidden layers, transfer functions, learning rate, and epochs.

Parameter	Value/name
Hidden layer sizes	3
Activation functions	<i>tansig</i>
Training function	<i>trainlm</i>
Performance regularization	0.2
Number of epochs	10

diameter and Z-potential have been shown to have a more important role in bubbles' durability and radical generation than frequency [88,89]. Finally, combinations with higher values of Tot_{score} were selected.

2.3.4. Hydrodynamic cavitation testing for humic acid and APIs' degradation

The performance of the selected Venturi tube (Design 6) for the degradation of humic acid and the selected APIs was investigated using the HC system (i.e., system 2) described in Section 2.3.2 and shown in Fig. 3.

The HC system was tested separately for the degradation of HA (starting concentration of 4 mg/L) and a mixture of the selected APIs (starting concentration of 200 µg/L for each API).

The effect of the presence of additional oxidant was tested at a substance:oxidant molar ratio of 1:230 [36,90], by adding the appropriate quantity of a PS and H₂O₂ in MilliQ stock solution (135 and 127 g/L, respectively), immediately after the system reached the operating pressure of 4 bar; pH of the solution to be treated was manually adjusted to ca. 2.0 using a 1.37 M H₂SO₄ solution. During each test, 14.5 mL samples of the treated solution were taken after every 5 min until 20 min and then every 20 min until 120 min. Moreover, in order to quench residual oxidant, 0.5 mL of a 12.3 mM Na₂SO₃ solution were added to each sample (Na₂SO₃:PS molar ratio of 22:1, and Na₂SO₃:H₂O₂ molar ratio of 195:1) [48–50].

2.3.5. Batch tests without cavitation

To assess the extent to which the degradation of HA and APIs could be specifically attributed to HC, a series of batch tests was conducted in triplicate to ensure reproducibility. Experiments were performed using 40 mL of each solution in 50 mL HDPE tubes, which were heated simultaneously in a water bath to maintain thermal homogeneity.

Temperature was monitored and controlled using a thermocouple connected to a heated stirring plate. Sample mixing was maintained using 6 mm magnetic stir bars rotating at approximately 250 RPM. The solutions were heated for 120 min across a temperature range consistent with pilot-scale observations (21–35 °C). This involved an initial heating rate of roughly 0.35 °C/min for the first 40 min, followed by a steady-state period at 35 °C. Concentrations were measured at the beginning and end of each test.

3. Results and discussion

3.1. Venturi tube design and testing

Results of preliminary testing with Venturi tube prototypes (i.e., nanobubbles' frequency, average hydrodynamic diameter, and Z-potential), along with the characteristics of each configuration (i.e., D_t , L_1 , L_2 , and α), are shown in Table 4 and Fig. 5.

Considering the nanobubbles' characteristics, the results showed that prototype 6 produced the best results: 89.7% of the produced bubbles were below 1 µm, with an average hydrodynamic diameter of 151 nm and a Z-potential of −15.4 mV. This prototype (i.e., $D_t = 1$ mm, $L_1 = 9.85$ mm, $L_2 = 72.85$ mm, and $\alpha = 1.96^\circ$) was then built from duplex stainless steel (ASTM A240 UNS S32205) to carry out further tests without the potential release of chemicals (e.g., PFAS) into water.

As shown in Table 4 and Fig. 5, reducing D_t leads to smaller, more frequent nano-bubbles. This occurs because the fluid is forced through a narrower section, increasing its velocity. According to the continuity equation (Eq. 12) the product of cross-sectional area (A) and velocity (v) remains constant along a streamline. Moreover, Bernoulli's equation (Eq. 13) (where P is static pressure, ρ the liquid density, and h the height of the liquid from a reference point), implies that this velocity increase causes a drop in static pressure (P), which—combined with high shear forces—promotes bubbles nucleation. However, when a high convergence angle (α) is also present, the resulting turbulence may cause bubbles to coalesce or collapse, partially negating the benefits of increased shear force [91].

$$A_1 \cdot v_1 = A_2 \cdot v_2 \quad (12)$$

$$P + \frac{1}{2} \rho v^2 + \rho gh = \text{constant} \quad (13)$$

Similarly, a longer L_1 can provide the necessary residence time for the flow to develop a stable shear profile, promoting the stabilization of

Table 4

Characteristics of the bubbles produced using the prototype Venturi tubes.

Prototype	D_t (mm)	L_1 (mm)	L_2 (mm)	α (°)	Bubble diameter (nm)	Frequency (%)	Z-potential (mV)
20	1.0	4.15	67.15	2.14	101 ± 4	60 ± 7	−18.1 ± 0.7
12	1.0	4.15	72.85	1.96	448 ± 15	67 ± 15	−14.7 ± 1.3
22	1.0	9.85	67.15	2.14	357 ± 11	72 ± 14	−16.8 ± 0.8
6	1.0	9.85	72.85	1.96	152 ± 3	90 ± 7	−15.4 ± 1.1
21	1.5	4.15	70.00	2.05	166 ± 5	60 ± 22	−18.9 ± 0.7
18	1.5	7.00	64.3	2.05	609 ± 38	33 ± 12	−21.3 ± 1.5
24	1.5	12.7	70.00	2.05	333 ± 11	71 ± 2.2	−22.9 ± 1.2
3	1.5	7.00	70.00	2.05	475 ± 52	37 ± 21	−15.4 ± 0.6
7	2.0	4.15	67.15	1.96	693 ± 54	39 ± 23	−18.2 ± 0.4
5	2.0	9.85	72.85	2.14	473 ± 15	64 ± 19	−23.0 ± 0.4

the gas-liquid interface. Specifically, bubbles exhibit a negative zeta potential primarily due to the preferential adsorption of hydroxide ions (OH^-) at the gas-liquid interface [92]. According to the adsorption mechanisms described by Takahashi et al. (2005) [93] and Beattie et al. (2004) [94], water molecules at the gas-liquid interface orient their hydrogen atoms toward the liquid phase to maximize hydrogen bonding. This disruption of the bulk hydrogen-bonding network creates an interfacial potential that energetically favours the accumulation of hydroxide ions while repelling H^+ cations. Furthermore, a shorter L_2 limits the time available for bubbles to coalesce, which reinforces a high frequency of bubble formation and maintains smaller bubble sizes. Conversely, if L_2 is excessively short, the residence time may be insufficient for this ionic adsorption process to reach equilibrium, resulting in a less negative zeta potential at the bubble surface.

3.2. Neural network modelling of nanobubble characteristics from tested Venturi tube designs

In order to assess the influence of Venturi geometry on nanobubble generation when using Venturi tube configurations that were not built due to manufacturing and budget constraints, a feed-forward neural network was developed based on the results of the built prototypes. In detail, the results of the regression and fitting are illustrated in Fig. 6, showing coefficient of determination (R^2) for the training and test set of 0.80 and 0.69, respectively, with an overall regression coefficient of the model of 0.74.

Fitting charts reporting predicted vs. actual (target) values are used to assess model performance, helping to detect overfitting (good training but poor testing performance) or underfitting (poor performance on both sets) by evaluating prediction accuracy across samples [95]. In detail, as shown in Fig. 6, the model performed well overall (i.e., global $R^2 = 0.74$) for nanobubble frequency and Z-potential, while it was less effective in predicting bubble hydrodynamic diameters, indicating the need for additional tests to better clarify the relationship between Venturi geometry and bubble size. This is reflected in a global R^2 of 0.74 and an RMSE of 151 nm, which represents nearly 20% of the full data range (100–700 nm). Given these metrics, model predictions regarding nanobubbles' diameter changes should be considered only as indicative, underscoring the necessity for further prototypes' testing to enhance model reliability.

Furthermore, root mean squared error (RMSE) for each output (i.e., nanobubbles hydrodynamic diameter, frequency, and Z-potential) was also used to test the model's performance regarding both the training and test set (Table 5). The acceptable range for RMSE values differs based on the studied topic, however for small datasets RMSE values corresponding to up to less than 20% of each input's range are considered acceptable [96]. In detail, since the ranges in the experimental data were: i) from ca. 100 to 700 nm for hydrodynamic diameter, ii) from ca. 30 to 90% for frequency, and iii) from ca. 15 to 23 mV for Z-potential, acceptable RMSE values would be below ca. 120 nm, 12%, and 1.6 mV, respectively. RMSE results also showed good performance for frequency and Z-potential (i.e., RMSE of 9.9% and 1.4 mV, respectively), while the

overall prediction accuracy for diameter was slightly below the acceptable range (i.e., RMSE of 131 nm).

In detail, while the training process was managed to strictly avoid overfitting [81–83] based on literature on neural networks for small experimental datasets, these results indicate the need for additional prototypes, as testing in this study was limited due to manufacturing and budget constraints.

The correlation between predicted and actual values for bubble diameter, frequency, and Z-potential was also evaluated (Table 6). Results revealed both positive and negative correlations, suggesting that trade-offs between nanobubble properties must be considered when selecting the optimal Venturi tube configuration for a specific application. For instance, de Medeiros and Baltar (2018) [97] observed that in mineral flotation, smaller bubble diameters are more effective than higher Z-potential. In our study, bubble diameter showed a negative correlation with both frequency and Z-potential, indicating that within the tested range (ca. 100–600 nm), smaller bubbles tend to have less negative Z-potential and be less frequent [98].

As shown in Table 7, the neural network optimization identified the following Venturi tube configuration as the most effective: (i) $D_t = 0.5$ mm, (ii) $L_1 = 10.68$ mm, (iii) $L_2 = 75.70$ mm, and (iv) $\alpha = 1.88^\circ$. For this configuration, the model predicted the generation of nanobubbles with an average hydrodynamic diameter of 90.4 nm, a frequency of 89%, and a Z-potential of −14.81 mV. Consistent with the correlation results, this suggests that a moderate decrease in Z-potential represents a necessary trade-off to achieve an approximately 40% reduction in nanobubble diameter. Notably, the reduced throat diameter required for this configuration could only be achieved using laser drilling technology, underscoring the importance of advanced manufacturing and precise design in enhancing cavitation-based treatment performance.

However, it is important to note that such a configuration, while enhancing nanobubbles production, would also reduce the water flow rate to one-fourth of the flow (i.e., ca 20 vs 80 L/h) of the optimal design suggested by the DoE approach. For this reason, among the neural network predictions, the configuration with the highest overall score among those with a 1 mm throat diameter was investigated. This design was then compared to the original DoE-optimized configuration to evaluate whether improvements in bubble characteristics could be achieved by altering other geometric parameters while keeping the same water flow.

In detail, this configuration ($D_t = 1$ mm, $L_1 = 8.67$ mm, $L_2 = 75.7$ mm, $\alpha = 1.88^\circ$) resulted in a ca. 5% reduction in bubble diameter (from 151 to 144 nm), a ca. 1% increase in Z-potential value (from −15.4 to −15.3 mV) and a slight drop in bubble frequency (from 89% to 83%) by shortening L_1 by 12%, increasing L_2 by 4%, and decreasing the convergence angle α by 4% (Table 8). These results suggest that small geometric adjustments, without changing the throat diameter, can improve bubble size while maintaining acceptable trade-offs.

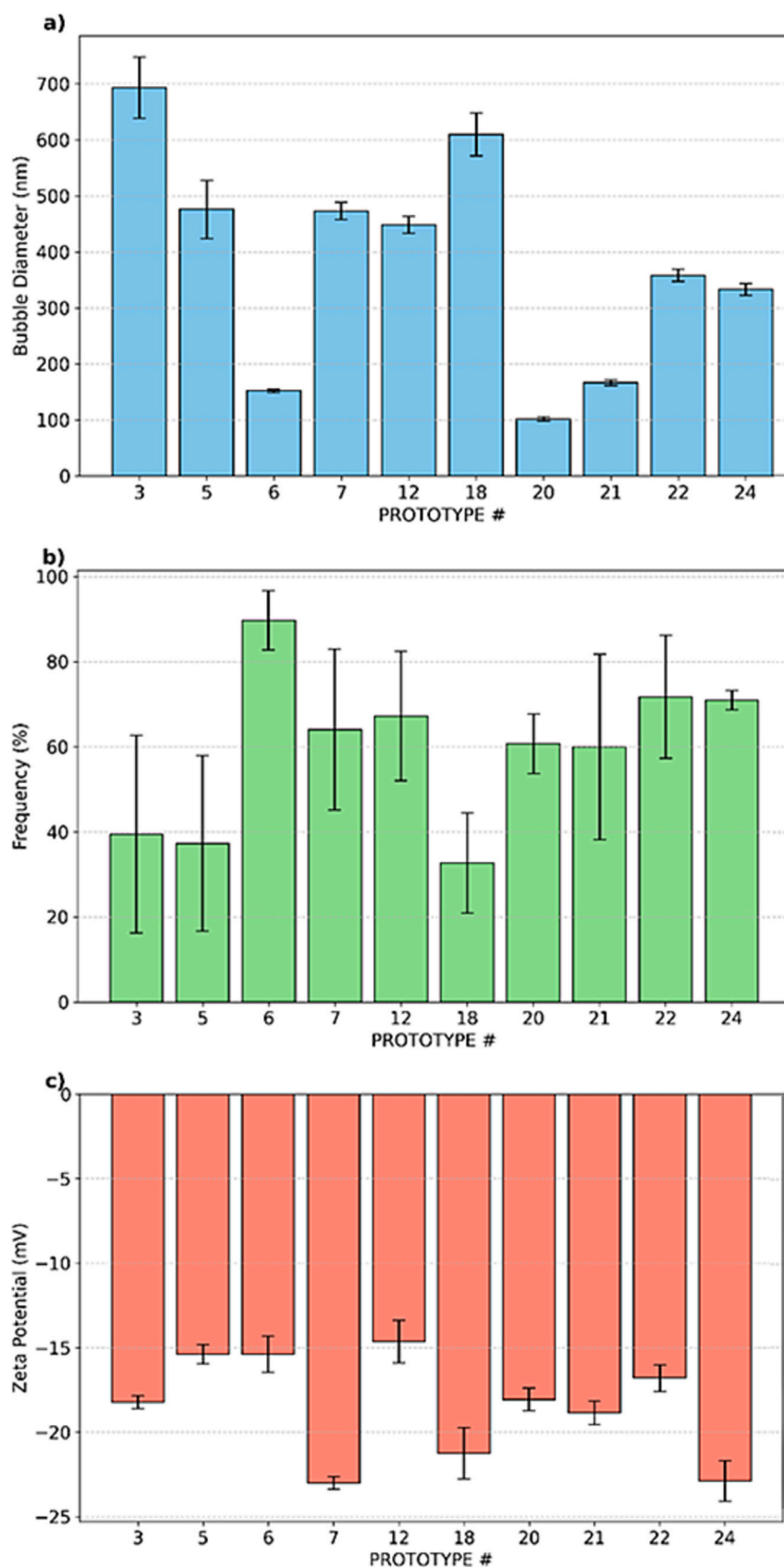


Fig. 5. Average bubbles' diameter (a), frequency (b), and Z-potential (c) for each prototype. Error bars represent the standard deviation of the results.

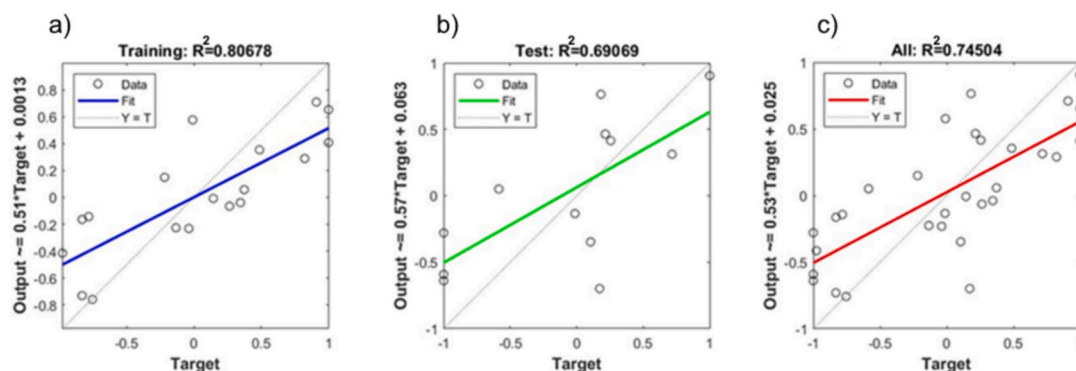


Fig. 6. Output vs Target values for training (a), test (b), and overall performance (c).

Table 5

Overall RMSE values of the developed neural network.

Output	RMSE		Overall model
	Training	Test	
Diameter (nm)	122	180	151
Frequency (%)	10.8	9.1	9.9
Z-potential (mV)	1.3	1.5	1.4

Table 6

Correlation coefficients (R) between actual and predicted values.

	Diameter (nm)	Frequency (%)	Z-potential (mV)
Diameter (nm)	1	−0.6	−0.7
Frequency (%)	−0.6	1	0.5
Z-potential (mV)	−0.7	0.5	1

Table 7

Comparison between nanobubble characteristics obtained from the optimized Venturi tube design based on DoE and neural network results.

Parameters	DoE suggested design ($D_t = 1$ mm, $L_1 = 9.85$ mm, $L_2 = 72.85$ mm, $\alpha = 1.96^\circ$)	Neural network suggested design ($D_t = 0.5$ mm, $L_1 = 10.43$ mm, $L_2 = 75.7$ mm, $\alpha = 1.88^\circ$)
Diameter (nm)	151	90
Frequency (%)	89	89
Z-potential (mV)	−15.4	−14.8

Table 8

Comparison between nanobubble characteristics obtained from the optimized Venturi tube design based on DoE and neural network results keeping a throat diameter of 1 mm.

Parameters	DoE suggested design ($D_t = 1$ mm, $L_1 = 9.85$ mm, $L_2 = 72.85$ mm, $\alpha = 1.96^\circ$)	Neural network suggested design ($D_t = 1$ mm, $L_1 = 8.67$ mm, $L_2 = 75.7$ mm, $\alpha = 1.88^\circ$)
Diameter (nm)	151	144
Frequency (%)	89	83
Z-potential (mV)	−15.4	−15.3

3.3. Modelling of nanobubbles' characteristics with different Venturi configurations using ANN

RSM was initially employed to investigate and quantify the relationship between Venturi tube geometrical parameters and nanobubble characteristics using polynomial regression models. However, despite testing multiple polynomial formulations, the resulting RSM models consistently exhibited poor statistical performance, as evidenced by overall model p -values exceeding the conventional significance threshold ($p > 0.05$) and low F-statistics close to unity. These findings indicate that low-order polynomial response surfaces were insufficient to capture the complex, nonlinear relationships between the input parameters and nanobubble characteristics. Consequently, an ANN-based approach was adopted to overcome these limitations and to more effectively resolve nonlinear interactions among the variables.

In total, 104,976 data points comprising four inputs (D_t , L_1 , L_2 , and α) and three outputs (nanobubble hydrodynamic diameter, frequency, and Z-potential) were used to generate 3D surfaces illustrating the relationship between each output and pairs of input variables (e.g., L_1 and L_2 with respect to Z-potential).

It was observed that the throat diameter (D_t) was the most influential parameter with respect to all model outputs, though its effect varied depending on the target design parameter. For nanobubble frequency, smaller D_t values (i.e., <1.5 mm) led to higher nanobubble frequencies (i.e., $>60\%$), likely due to increased fluid velocity and shear pressure at the constriction, which promoted cavitation (Fig. 7a). Moreover, while bubble size estimations were affected by significant uncertainty, the model still showed a noticeable increase of bubbles diameters with larger D_t , as lower shear pressure downstream of a wider throat allows bubbles to grow without collapsing prematurely, giving the bubbles' diameter sufficient time to increase before bursting (Fig. 7b).

Moreover, D_t exhibited a coupled effect with L_2 on Z-potential (Fig. 7d). Specifically, while smaller diameters favour more intense cavitation and increased interfacial area, a more negative Z-potential was observed only when L_2 was sufficiently long to allow hydroxyl radicals to be absorbed onto the bubble surface. For instance, when D_t was within 1–2 mm, increasing L_2 from 64 to 72 mm resulted in a Z-potential shift of approximately -1.5 to -5 mV, indicating enhanced interfacial activity due to sustained shear stress and gradual pressure recovery. In contrast, L_1 had a negligible influence on Z-potential, as its role in shaping upstream flow does not significantly affect surface charge formation (Fig. 7e) [99].

Furthermore, L_1 showed minimal influence on frequency, consistent with the fact that cavitation initiates primarily at the Venturi's throat. However, it played a minor role in modulating bubble size, particularly within the intermediate D_t range (1–2 mm), where longer L_1 produced larger bubbles (Fig. 7b). This effect can be attributed to improved flow stabilization upstream of the throat, resulting in more consistent cavitation development [71]. The influence of L_1 also became more

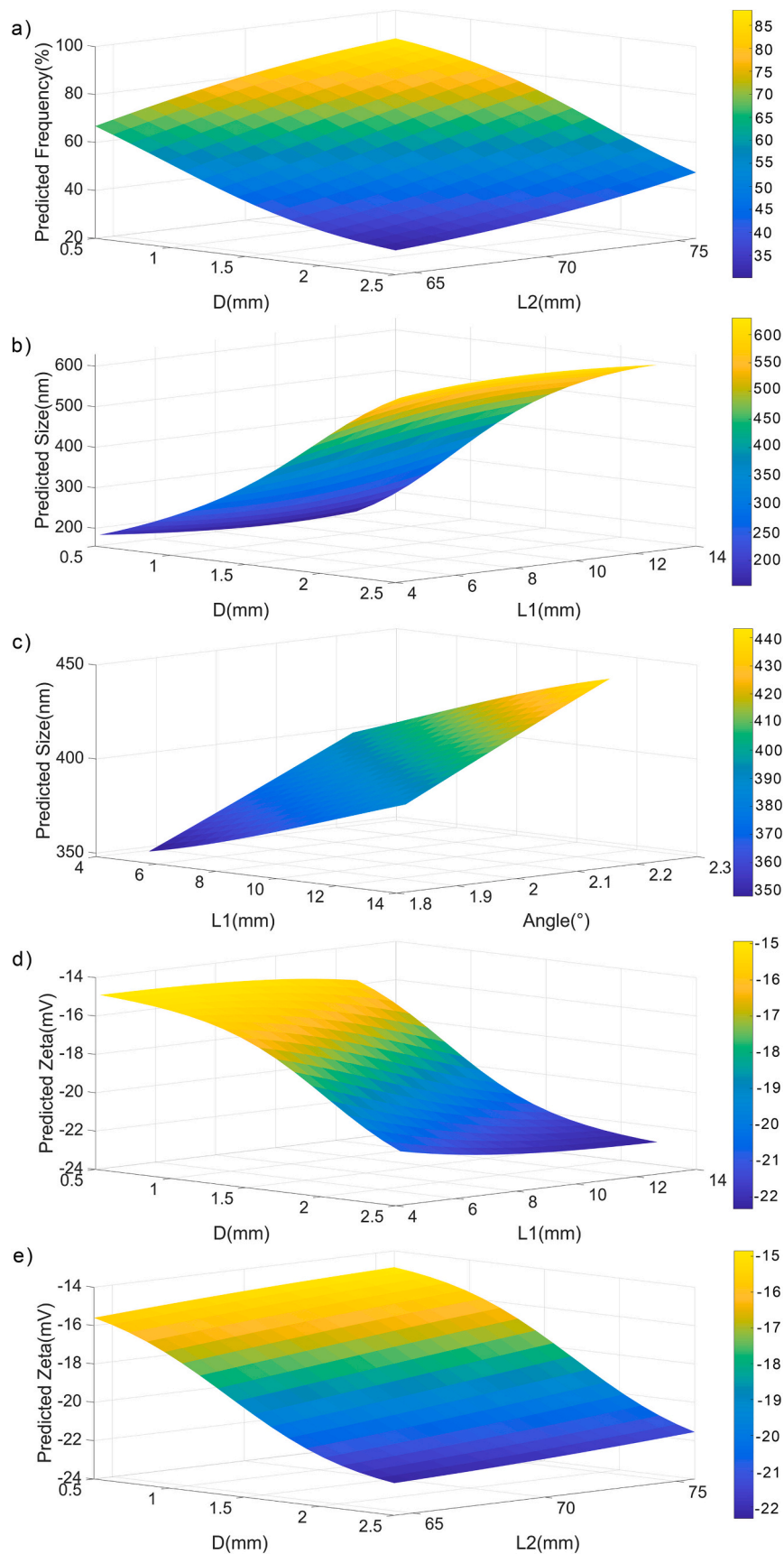


Fig. 7. 3D surfaces depicting the relationship between Venturi tube parameters and bubbles' characteristics: predicted frequency (%) vs D_1 and L_2 (a); predicted size (nm) vs D_1 and L_1 (b); predicted size vs L_1 and angle (c); predicted Z-potential vs D_1 and L_1 (d); predicted Z-potential vs D_1 and L_2 (e).

pronounced when combined with higher convergence angles, owing to enhanced residence time and flow conditioning (Fig. 7c). Similarly, L_1 exhibited limited direct influence on Z-potential. Across all D_t ranges (0.5–2.5 mm), shorter L_1 values led to slightly less negative Z-potentials. This effect can be explained by excessive turbulence in the upstream region, which reduces the interaction time between bubbles and hydroxyl radicals, thereby limiting surface charge stabilization (Fig. 7d). In detail, changes of L_1 yielded an increase of the overall score of ca. 4.3%/cm, corresponding to a minimum significant variation of ca. 0.108 cm. Furthermore, the increase of D_t reduced the overall score by ca. 0.7%/mm, corresponding to a minimum significant variation of 0.025 mm.

The convergence length (L_2) and angle (α) primarily influenced downstream dynamics and exhibited contrasting effects on the outputs. Specifically, L_2 increased frequency, particularly at lower D_t , likely due to extended low-pressure regions that promote cavitation (Fig. 7a). However, it also increased bubble size, as longer recovery zones favour bubble coalescence and collapse (Fig. S1a). In detail, changes of L_2 resulted in an increase of the overall score of ca. 2.8%/cm, corresponding to a minimum significant variation of 0.144 cm. Moreover, Z-potential, was primarily governed by α , D_t , and L_2 , with minimal contribution from L_1 (Fig. 7e). When combined with L_1 and D_t , increasing α led to more negative Z-potential values (Fig. S1a-b). This effect can be attributed to sharper angle convergence which intensifies shear stresses and promote partial bubble collapse, thereby increasing the gas-liquid interfacial area. The expanded interface enhances $\text{OH}^\cdot$ adsorption onto bubble surfaces, resulting in a more negative Z-potential. However, the effect of changes in α values was lower than the other design parameters, with an increase of the final score of ca. 7.5% $^\circ$, corresponding to a minimum significant variation of 0.05 $^\circ$.

To further explore the role of D_t in influencing bubble characteristics, a sensitivity analysis was performed. While the other parameters were fixed at their optimized conditions (i.e., $L_1 = 8.67$ mm, $L_2 = 75.7$ mm, $\alpha = 1.88^\circ$), D_t was varied between 0.5 and 2.5 mm with increments of 0.1 mm to reflect practical manufacturing constraints, despite the theoretical statistical significance threshold of 0.025 mm (Table S6 and Fig. S2). In detail, the sensitivity analysis revealed a distinct critical threshold regarding the influence of the throat diameter (D_t) on bubble characteristics. In the lower range, specifically where $D_t \leq 1$ mm, changes in diameter resulted only in marginal variations across all three

parameters. As D_t exceeded 1.0 mm, the sensitivity of the system increased markedly. In detail, the rate of bubble growth accelerated significantly, while the decline in both frequency and Z-potential became much steeper. This trend intensified further past $D_t = 1.3$ mm, indicating that the interval between 1.3 mm and 2.5 mm represents the region of highest sensitivity, where even minor adjustments to the throat geometry yield the most substantial alterations in bubble size, generation rate, and Z-potential.

3.4. Overall removal of HA and APIs

Control batch experiments results showed less than 3% degradation for all compounds, indicating a negligible effect of the added oxidants in the absence of HC. Accordingly, any degradation observed under operating conditions was primarily attributed to cavitation-induced generation and activation of reactive radicals.

As reported in Table 9, under neutral conditions (pH = 7.4) and without the addition of external oxidants, the degradation of all selected compounds after 120 min remained below 5%. This outcome is consistent with previous findings regarding the short lifetime of hydroxyl radicals under neutral conditions [100]. However, the hydrophobicity of the target compounds must also be considered, as it strongly influences their partitioning between the bulk liquid and the gas-liquid interface, where radical generation and subsequent reactions predominantly occur [101].

Based on these results, the system was subsequently tested under acidic conditions (pH = 2). Although such acidification imposes additional operational constraints for real-world upscaling (e.g., post-treatment neutralization, use of acid-resistant materials, and reagent consumption), it was nevertheless fundamental to obtain significant degradation [102]. Specifically, acidification has been shown to both increase radical stability and promote the coalescence of bubbles into larger cavities [93]. This behavior is attributed to the partial neutralization of the negative charge at the gas-liquid interface (i.e., a less negative Z-potential), thereby reducing electrostatic repulsion between bubbles. Although larger bubbles are generally considered less efficient at radical production due to lower collapse intensities, the enhanced degradation observed in this study suggests that the increased stability of the radicals more than compensates for the pH-induced increase in

Table 9

Results of HA and selected API degradation tests with and without oxidant addition.

Compound	HC conditions *	Additional oxidant-driven step: duration (min)	Additional oxidant-driven step: 5-min degradation rate ($\mu\text{mol}/\text{min}$)	HC-driven step: 1st degree kinetic rate constant (1/min)	Degradation after 120 min (%) **
Climbazole ^b (CLI)	HC	–	0.05 ^a	0.0006 (R^2 : 0.92)	6
	HC + PS	15	1.0	0.0035 (R^2 : 0.99)	65
	HC + H_2O_2	5	1.1	0.0014 (R^2 : 0.99)	42
	HC	–	–	–	< 5
Sulfadiazine ^b (SLD)	HC + PS	15	1.8	0.0078 (R^2 : 0.99)	88
	HC + H_2O_2	5	2.2	0.0010 (R^2 : 0.95)	68
Sulfamethazine ^b (SLM)	HC	–	–	–	< 5
	HC + PS	15	0.3	0.0065 (R^2 : 0.96)	54
	HC + H_2O_2	5	0.4	0.0060 (R^2 : 0.99)	44
Sulfapyridine ^b (SLP)	HC	–	–	–	< 5
	HC + PS	15	0.6	0.0054 (R^2 : 0.91)	56
	HC + H_2O_2	5	0.7	0.0042 (R^2 : 0.99)	43
	HC	–	–	–	< 5
Venlafaxine ^b (VEN)	HC + PS	15	0.6	0.0083 (R^2 : 0.98)	69
	HC + H_2O_2	5	0.6	0.0038 (R^2 : 0.99)	47
	HC	–	0.0002 ^a	0.0033 (R^2 : 0.91)	32
Humic acid ^b (HA)	HC + PS	15	0.01	0.0038 (R^2 : 0.93)	60
	HC + H_2O_2	5	0.02	0.0013 (R^2 : 0.94)	58

^a : Refers to the first five minutes of the HC-driven step, as no additional oxidant was present.

^b : The initial concentration was 200 $\mu\text{g}/\text{L}$ for all APIs (CLI, SLD, SLN, SLP, and VEN) and 4 mg/L for HA. Degradation in the absence of HC (with and without additional oxidants) was less than 3% for all compounds.

* : All tests reported in this table were conducted at pH 2.0. Under neutral conditions (pH 7.4) and without additional oxidants, HC consistently resulted in less than 5% degradation after 120 min.

** : Degradation reported for HA refers to mineralization, whereas degradation reported for APIs refers to primary degradation.

bubble size.

When HC was applied under acidic conditions ($\text{pH} = 2$) without oxidants, HA showed ca. 30% removal, whereas APIs were removed only to a significantly lower extent. This difference can be primarily attributed to concentration effects, as the initial concentration of HA (i.e., 4 mg/L) was 20 times higher than that of the APIs (i.e., 200 $\mu\text{g/L}$). At higher concentrations, diffusion limitations are less critical, as the half-life of hydroxyl radicals is sufficient for interaction with HA, while at lower concentrations the probability of pollutant molecules encountering available radicals is reduced [103]. However, it should be noted that excessively high initial concentrations have been reported to decrease performance due to: i) excessively high pollutant-to-radical ratios, resulting in complete radical consumption before full degradation can occur; and ii) the accumulation of intermediate products, which compete with parent compounds for radicals and thereby limit primary degradation [35,104].

Among the APIs, CLI was the only compound exhibiting detectable degradation under acidic HC conditions without oxidants (ca. 6%), whereas sulfonamide antibiotics and VEN showed negligible removal (Fig. 8). This behavior can be attributed to several factors, such as differences in the hydrophobicity of the compounds, their limited volatility, and their chemical structure. In detail, CLI exhibits a significantly higher hydrophobicity ($\log K_{\text{ow}} = 3.83$), compared to SLD, SLM, and SLP (i.e., $\log K_{\text{ow}} = \text{ca. } -0.1$ to 0.5) (Fig. 1). In HC systems, hydrophobic compounds preferentially accumulate at the gas–liquid interface, where local radical concentrations are highest and pyrolytic effects may occur [105]. Conversely, hydrophilic compounds remain predominantly in the bulk solution, where radical interactions are limited in the absence of external oxidants. The very low Henry's law constants for all tested APIs ($<10^{-3} \text{ Pa}\cdot\text{m}^3/\text{mol}$) also show that volatilization into the bubbles is probably negligible, minimizing the contribution of pyrolytic degradation. Furthermore, the limited degradation of all tested APIs save for CLI, could also be related to the presence of electron-deficient hetero-aromatic structures (e.g., sulfonamides), electron withdrawing substituents (e.g., halogens), and sterically hindering groups (e.g., alkyl chains or *N*-methyl substituents), all of which reduce their susceptibility to radical oxidation.

As shown in Fig. 8, the addition of oxidants (i.e., PS and H_2O_2) under acidic conditions significantly enhanced degradation. Overall, PS was more effective than H_2O_2 , which can be attributed to the longer half-life of sulfate radicals (ca. 35 μs) compared to hydroxyl radicals (ca. 20 ns) [106], as well as their higher selectivity toward electron-transfer reactions with aromatic systems [107].

Among the investigated sulfonamide antibiotics, the highest degradation was observed for SLD, reaching approximately 88% with PS and 68% with H_2O_2 , whereas SLM and SLP exhibited lower removal efficiencies (ca. 55% and 44%, respectively, with PS and H_2O_2). These

differences can be attributed to variations in protonation state at $\text{pH} = 2$ as well as to distinct structural and electronic properties. Although the reactivity of the compounds toward hydroxyl radicals is comparable (i.e., k_{OH} ca. $6\text{--}7 \cdot 10^9 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ [108]), at the experimental pH ($\text{pH} = 2$) SLD (pK_a of 2.1) exists as a mixture of neutral and protonated species, whereas SLM (pK_a of 2.65) is predominantly protonated. Since electrophilic radicals react more rapidly with neutral, electron-rich species than with protonated, electron-deficient cations, the higher fraction of neutral SLD results in faster degradation. Moreover, molecular structure further influences reactivity. In detail, SLD contains a pyrimidine ring with two nitrogen atoms, which promotes greater delocalization of electron density from the sulfonamide and amino substituents, promoting electrophilic attack by sulfate radicals as well as hydrogen abstraction or hydroxylation by hydroxyl radicals. In contrast, SLM contains two methyl substituents on the pyrimidine ring, increasing steric hindrance around the sulfonamide group and donating electron density that reduces electrophilic susceptibility. Although SLP exhibits a pK_a similar to that of SLD (pK_a of 2.2), it contains a pyridine ring that is intrinsically more electron-deficient due to the presence of a ring nitrogen atom, resulting in fewer reactive sites for radical attack and limited resonance stabilization of reaction intermediates.

The tested HC system exhibited comparable degradation performance for CLI and VEN, achieving approximately 65% removal with PS and 45% with H_2O_2 . These degradation levels were lower than those observed for SLD but higher than for SLM and SLP. Despite their relatively high hydrophobicity ($\log K_{\text{ow}} > 3$), which favours accumulation at the bubble interface where radical concentrations are highest, VEN and CLI (pK_a of ca. 8.9 and 6.5, respectively) are fully protonated at the experimental pH. This positive charge, together with the presence of electron-withdrawing substituents (e.g., chlorine and tertiary amine groups) and steric constraints that limit radical accessibility, deactivates aromatic rings toward radical attack. Nevertheless, interfacial accumulation likely partially compensated for the reduced intrinsic reactivity associated with protonation and molecular structure.

To the best of the authors' knowledge, no other nanobubble-based HC systems have been applied at the pilot scale for the degradation of the selected organic chemicals. Nevertheless, comparisons with studies employing conventional HC-based systems provide valuable insight into the potential of nanobubble-assisted HC for water and wastewater treatment. Reported results for cavitation-assisted oxidation processes targeting HA and the selected APIs vary widely and are strongly influenced by reactor configuration, initial concentration (C_0), and the use of external energy sources (e.g., ultrasound, UV irradiation) or additional oxidants (e.g., H_2O_2 , PS, magnesium sulfate, NaOCl, ozone).

For HA removal, Araujo et al. (2020) [90] reported 16% mineralization using a microbubble-based HC system without oxidants, compared to 12% in the present work. Moreover, while removal rates

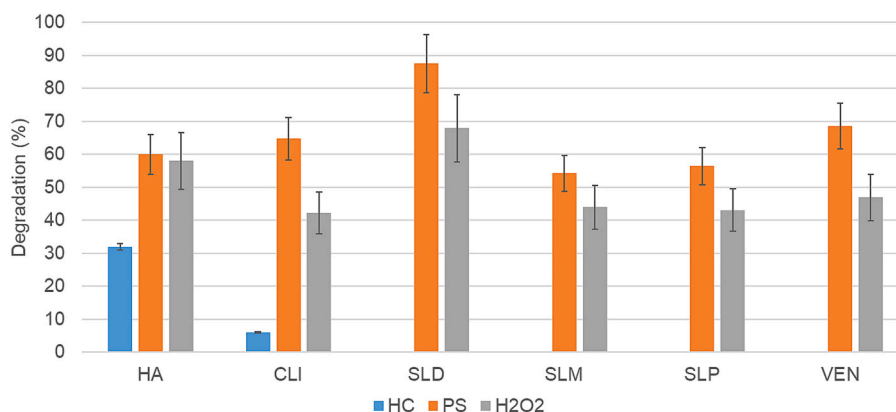


Fig. 8. HC performance for the degradation of HA and APIs at $\text{pH} = 2.0$, with and without the presence of additional oxidants (i.e., PS and H_2O_2). Results for HA are reported as mineralization, while results for CLI, SLD, SLM, SLP, and VEN refer to primary degradation.

were almost similar, the operational conditions differ significantly (9 L vs 14 L, 7.3 bar vs. 4 bar, and ca. 204 W/L vs. ca. 93 W/L for Araujo et al. (2020) and our work, respectively), demonstrating that our work maintains comparable mineralization at a larger scale with less than half the energy consumption. However, when considering H_2O_2 -assisted treatment, the higher HA degradation obtained in this work (58 vs 36%) could not be ascribed only to the use of nanobubbles since the oxidant dosage used in our work was higher than the one used by Araujo and co-workers (230:1 vs 10:1 H_2O_2 :HA ratio).

Furthermore, Wang et al. (2015) [34] demonstrated that PS activation using cavitation-based systems is highly thermally dependent using a 100 mL ultrasound-assisted system (pH = 3, ca. 2000 W/L at 40 kHz, 120 min), with HA mineralization rising from <10% at 30 °C to ca. 90% at 50 °C. Although this method achieved high efficiencies, it necessitated a considerable energy input and a high oxidant dosage (924:1 PS:HA ratio). In contrast, while our work reached lower overall degradation, it showed the potential of using nanobubble-based cavitation for PS thermal activation by reaching 62% HA removal at significantly lower temperature (35 vs 50 °C), lower energy input (ca. 93 W/L vs ca. 2000 W/L), and lower oxidant consumption (230:1 vs 924:1 PS:HA ratio).

Čehovin et al. (2016) [109] reported a maximum HA mineralization of 31% using a pilot-scale UV/ H_2O_2 -assisted HC system (83 L, 75 W UV, 1.18 kW total power, 3.5:1 H_2O_2 :HA ratio, pH = 7.7, 6–8 bar, 60 min). While their setup operated at a larger volume with lower total energy input (31 W/L vs. 93 W/L) than ours, their lower treatment efficiency can be partially attributed to a significantly lower oxidant dosage and the use of tap water, as it contains several substances that can act as radical scavengers (e.g., carbonate, sulfate, and chlorine ions). In contrast, our nanobubble-based process achieved ca. 58% HA mineralization at lower pressure (4 vs 6–8 bar) and without UV radiation, but with higher oxidant and energy consumption, highlighting tradeoffs between degradation efficiency, system complexity, and energy and chemical consumption.

Several works have also reported on the use of cavitation-based systems for API degradation. For example, Cai et al. (2019) [43] reported rapid CLI removal (>95% in <5 min) in a 400 mL UV/chlorine batch reactor (pH = 7.0, 20:1 chlorine:CLI ratio, C_0 = 2.9 mg/L, 4.36 mW/cm² UV intensity). In detail, while the UV-driven process exhibited faster degradation compared to the present study, it required high energy inputs and also showed a sensitivity to matrix effects, with removal rates dropping from ca. 0.01 to 0.06 1/s from neutral alkaline conditions (pH = 9) and from ca. 0.01 to 0.002 1/s from river water to a WWTP secondary effluent.

In addition, other studies have investigated the combination of cavitation with additional catalysts (e.g., Fe^{3+} salts or $\alpha\text{-Fe}_2\text{O}_3$), oxidants (e.g., PS, and H_2O_2), and hybrid energy inputs (e.g., ultrasounds and UV) for the degradation of sulfonamide antibiotics. For instance, Roy and Moholkar (2022) [44] achieved 93% SLD removal in a 5 L HC system by coupling cavitation with $\alpha\text{-Fe}_2\text{O}_3$, PS, and H_2O_2 under acidic conditions (pH = 4, 1:9.1:17.4:47.5 SLD: $\alpha\text{-Fe}_2\text{O}_3$:PS: H_2O_2 ratio, 8 bar, C_0 = 20 mg/L, 90 min). While achieving higher removal efficiency than our work, this process required higher operating pressure (8 bar) and the activation of the hybrid Fenton-persulfate system required additional 90 min before the treatment of the SLD solution could begin, highlighting a trade-off between chemical/energy consumption, degradation efficiency, and treatment time compared to our nanobubble-based approach.

Similarly, Agarkoti et al. (2023) [45] reported ca. 94% sulfamerazine removal using a system that combined dual-frequency ultrasonic cavitation, UV irradiation, H_2O_2 , and Fe^{3+} salts (0.8:3.8:1 Fe^{3+} : H_2O_2 :sulfamerazine ratio, 5 L, 20 W/L ultrasonic power, pH = 3, 8 W UV light intensity, C_0 = 60 mg/L, 60 min). While the removals obtained in the present work for the selected sulfonamide antibiotics (i.e., SLD, SLP, and SLM) were slightly lower, they were achieved using a single oxidant and without the need for additional Fe sources, showing how nanobubble-assisted HC alone can achieve substantial pollutant removal under

milder, less energy- and reagent-intensive conditions.

In addition, Hollman et al. (2018) [110] reported >99% removal of VEN in a 200 mL UV/ H_2O_2 HC system (1:1 H_2O_2 :VEN ratio, 3619 W/m³ UV intensity, pH = 7.1, C_0 = 10 mg/L, 23 min). Although this UV-driven process exhibited faster kinetics and complete degradation, it relied on a high-intensity energy input (ca. 3.6 kW/m³) applied to a small volume, showing important tradeoffs between degradation performance and system scalability. While our nanobubble-based system obtained noticeably lower results, it offers a more scalable treatment approach operating under milder, catalyst-free conditions and without the need for UV.

AOPs have been shown to not always reach complete mineralization of the treated chemicals, leading to the formation of several degradation products. In detail, CLI degradation in hydroxyl-dominated systems, such as the UV/chlorine treatment shown in the work of Cai et al. (2019) [43], proceeds primarily through i) cleavage of ether bond between the chlorophenyl moiety and the imidazole group, ii) dechlorination of the aromatic ring, and iii) isomerization. These reactions were shown to mainly generate phenolic and rearranged intermediates, with limited progression toward mineralization. In contrast, as reported in the work of Liang et al. (2025) [111], PS-based systems were shown to lead to complete mineralization by means of ether cleavage, dechlorination, and oxidation of the tert-butyl substituent through alcohol and aldehyde-like intermediates.

Regarding sulfonamide antibiotics, several common degradation pathways have been observed starting from S—N or S—C bond cleavage. In particular, several works using PS-based AOPs [112–114] for SLD degradation showed the S—N sulfonamide bond cleavage as the main initial step, leading to the formation of 4-aminobenzenesulfonic acid and several heterocyclic amine fragments (e.g., 2-aminopyrimidine). This is generally followed by further oxidation, nitration, and ring-opening reactions of both fragments. The same studies [112–114] also report that the present hydroxyl radicals instead tend to primarily induce hydroxylation of the aniline ring or secondary oxidation of cleavage products. Similar degradation mechanisms were also observed for SLP, where in the presence of PS, degradation preferentially proceeded via direct S—N cleavage, but breaking of the S—C bond was also observed [115,116], generating aminopyridine and sulfonyl-derived intermediates. In contrast, in systems dominated by hydroxyl or chlorine radicals the S—C bond cleavage is anticipated by hydroxylation of the aniline moiety [117]. For SLM, multiple studies [118–120] reported three principal degradation routes in PS-activated systems: i) S—N bond cleavage, yielding heterocyclic amines and sulfonyl fragments; ii) Smiles-type rearrangements accompanied by SO_2 elimination, and iii) oxidation of the aniline moiety, forming hydroxylated, nitroso-, and nitro-substituted derivatives. Furthermore, the same studies showed that Smiles-type rearrangements rarely occurred in hydroxyl-radical-driven systems.

Degradation of VEN across PS-, H_2O_2 -, and hybrid oxidation systems was shown to typically start with O- and N-demethylation, followed by aromatic or alicyclic hydroxylation, dehydration, and progressive ring-opening reactions driven by reactive oxygen species [121–124]. In detail, PS-based system showed better mineralization performances, while hydroxyl radicals were usually limited to hydroxylation reactions, particularly on the benzene and cyclohexanol rings.

3.5. Degradation kinetics of HA and APIs

Kinetic analysis is essential to elucidate the underlying reaction mechanisms and rate-determining steps of a degradation process, allowing more effective removal optimization [125] and to better compare the effects of different testing conditions. In fact, several studies have shown that degradation occurs rapidly at the start of the process due to the high availability of radicals and target chemical molecules [126,127], then the reaction slows down due to mass transfer phenomena as the reactants become less concentrated [128–130].

Concentration of the target chemicals in the tank during each test was fitted against a pseudo first-order kinetic model (Table 9 and Fig. S3-S8), indicating the degradation of a single kinetic regime under cavitation alone, whereas the addition of an oxidant introduced two distinct kinetic phases. In detail, the initial step could be attributed to the activation of the added oxidants by HC, and its subsequent consumption, while the second step could be related to the continuous production of hydroxyl radicals through HC in the Venturi tube and to the activation of residual oxidant still present in the system [131,132]. The results showed that the first step for PS lasted about 3 times longer than for H₂O₂ (i.e., ca. 15 vs 5 min, respectively). This extended activity of PS could be attributed to several factors: i) slower activation of persulfate into sulfate radicals compared with the rapid decomposition of H₂O₂ into hydroxyl radicals [133], ii) the longer half-life of sulfate radicals relative to hydroxyl radicals [106], and iii) the higher selectivity of sulfate radicals, which minimizes side reactions with degradation byproducts and scavengers (e.g., background ions or impurities) [134].

To further investigate the two observed kinetic regimes, the initial degradation rate (μmol/min) during the first five minutes of each test and the pseudo-first-order kinetic constant (1/min) for the subsequent HC-driven phase were calculated (Table 9). A kinetic model was not fitted to the initial step due to the limited number of data points. It should also be noted that temperature profiles varied slightly among tests, thus the reported rates and constants should be considered as indicative.

Overall, results showed that the initial step was consistently faster with H₂O₂ than with PS across all compounds. This behavior can be attributed to the more rapid decomposition of H₂O₂ into hydroxyl radicals [135], resulting in a higher effective oxidant concentration during the first minutes of reaction. However, once the initial step concluded, degradation proceeded more rapidly with PS, likely due to a greater residual concentration of un-activated persulfate available to sustain sulfate radical generation. In detail, the highest initial rates were observed for SLD (1.8 and 2.2 μmol/min for PS and H₂O₂, respectively), CLI (1.0 and 1.1 μmol/min), and SLP (0.7 and 0.6 μmol/min), mirroring the overall removal trend (Fig. 8). When considering the pseudo-first-order kinetic constants for the HC-driven step, degradation with PS was consistently faster than with H₂O₂, ranging from approximately 1.1-fold for SLM to 7.8-fold for CLI. This trend can be attributed to the slower activation of PS into sulfate radicals [136], which results in a higher residual PS concentration that is gradually activated, thereby sustaining sulfate radical production over an extended period.

3.6. Energy efficiency and comparative analysis

Energy consumption is a critical parameter in the evaluation of water treatment technologies, as it directly affects operational costs, environmental sustainability, and the feasibility of large-scale implementation. To quantify the energy efficiency of the developed pilot-scale HC system, performance was assessed using two complementary metrics. Degradation yield (G, the mass of pollutant degraded per unit of energy (mg/kWh)) and calculated using Eq. 14.

$$G = \frac{(C_0 - C_t)V}{P \cdot t} \quad (14)$$

where C₀ and C_t are the initial and final concentrations (mg/L), V is the treated volume (m³), P is the power of the system (kW), and t is the treatment time (h).

To provide also a concentration-independent comparison, the Electrical Energy per Order (E_{EO}, energy required to reduce concentration by one order of magnitude per m³) was calculated, using Eq. 15:

$$E_{EO} = \frac{P \cdot t \cdot 1000}{V \cdot \log\left(\frac{C_0}{C_t}\right)} \quad (15)$$

Considering the system configuration that achieved the best results (i.e., HC + PS system), the observed yield for primary degradation of the APIs ranged from approximately 0.95 mg/kWh (SLD) to 0.46 mg/kWh (SLP), with an average of 0.70 mg/kWh for the whole mixture. While these values are lower than those reported in high-concentration studies, such as Agarkoti et al. (2023) [45] who achieved degradation yields >14 mg/kWh for sulfamerazine at C₀ = 15 mg/L, this difference can be attributed to diffusion limitations, as the initial concentration in the present study (0.2 mg/L) was 75 times lower than that used by Agarkoti and co-workers.

The HC + PS showed a degradation yield of 12.9 mg/kWh, even though HA mineralization was considered, which is an energetically more demanding process than primary degradation. This value is higher than the 4.5 mg/kWh reported by Wang et al. (2015), whose ultrasonic system (C₀ = ca 10 mg/L, 200 mL, 200 W), showing that the nanobubble-based HC configuration offered superior energy efficiency for HA treatment.

When considering E_{EO} evaluation, our system ranged between 202 kWh/m³ (SLD) to 761 kWh/m³ (SLP), with an average of 407 kWh/m³ for the whole mixture, while a value of 467 kWh/m³ was estimated for HA. These results are in line with other pilot-scale studies, matching the efficiency of hybrid HC-ultrasonic reactors reported by Agarkoti et al. (2023) [45] (300–400 kWh/m³). Furthermore, the system demonstrated efficiency comparable to the UV/H₂O₂ treatment of VEN reported by Hollman et al. (2018) [110] (300–1400 kWh/m³) and superior the ultrasonic mineralization of HA reported by Wang et al. (2015) [34] (>1000 kWh/m³).

4. Conclusions

In this study, we report on the development and evaluation of a pilot-scale (14 L) Venturi-based hydrodynamic cavitation (HC) system engineered to enhance nanobubble generation. The system was tested for the degradation of humic acid (HA) and five representative active pharmaceutical compounds (i.e., climbazole, sulfadiazine, sulfamethazine, sulfapyridine, and venlafaxine) in the presence of additional oxidants (sodium persulfate (PS) and hydrogen peroxide (H₂O₂)) but without additional energy inputs (e.g., ultrasonic transducers or UV irradiation) or catalysts.

From a design perspective, the application of response surface methodology (RSM) coupled with artificial neural network (ANN) modelling provided insights into the relationship between Venturi tube design and cavitation performance. We established a clear relation between the Venturi tube geometry and the resulting bubble dynamics, showing that specific geometric parameters can be adjusted to optimize the trade-off between nanobubble size, generation frequency, and Z-potential. This methodological framework offers a valuable predictive tool for engineering cavitation devices with specific hydrodynamic characteristics.

In terms of degradation performance, this study highlighted the distinct advantages of coupling nanobubble-based HC with specific chemical oxidants, with the best results obtained in the presence of PS. The results suggest that the energy released during cavity collapse effectively activates persulfate, generating a sustained release of sulfate radicals. This pathway proved significantly more stable under turbulent hydraulic conditions than the hydroxyl radical pathway associated with H₂O₂, which appeared susceptible to rapid scavenging or self-decomposition in this setup.

Ultimately, the combined benefits of this system—enhanced mass transfer via nanobubbles, reduced reagent consumption through targeted activation, and simplified reactor design—highlight its potential for industrial application. By bridging the gap between theoretical micro-scale studies and pilot-scale operation, this research confirms that nanobubble-assisted HC represents a viable strategy for the treatment of persistent organic pollutants in industrial water treatment applications.

CRediT authorship contribution statement

Saman Moftakhari Anasori Movahed: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Loris Calgaro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Giorgos Ioannou:** Visualization, Investigation, Formal analysis. **Laura Pagnin:** Visualization, Investigation, Formal analysis. **Ioannis Katsoyiannis:** Writing – review & editing, Supervision, Funding acquisition. **Antonio Marco-mini:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Ethics approval

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cej.2026.174827>.

Data availability

Data will be made available on request.

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