

Article

Design and implementation of an electrochemical sensor, based on a microfluidic system, to determine acetaminophen concentrations in water.

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Abstract: In order to address water quality control difficulties in remote locations, an electrochemical sensor is designed, manufactured and characterized to detect acetaminophen on aqueous solutions. CAD (Shapr3D) and PCB (Altium Designer) software tools were used in the design of the sensing electrodes. The characterization of the sensor was done by exposing the electrode to acetaminophen diluted in purified water and then measured the change in the output electrical signal through cyclic voltammetry.

Keywords: electrochemical sensors; microfluidic systems; cyclic voltammetry; acetaminophen.

1. Introduction

Pharmaceutical industries have been beneficial around the world. Nevertheless, medicine production and equipment maintenance generate pollutants that end up being deposited in waters. Despite cleaning processes at treatment facilities, most of these residues make their way to municipal water bodies and oceans. UNESCO conducted a study that traced 118 different drugs to find out only nine of these medications were filtered with an efficiency higher than 95% and around half of the analyzed products were only partially eliminated with an efficiency lower than 50% [1]. Furthermore, most studies to trace pharmaceutical products take place in a small number of countries (typically developed countries), and those studies do not consider areas of difficult access with low or no regulations regarding the disposal of these types of residues [2].

To illustrate the context of developing countries, Colombia, where 5'486,826 medicine prescriptions were made in 2020 according to Health Promotion Entities (EPS by the acronym in Spanish) [3], can be used to estimate the impacts of some pharmaceutical pollutants like acetaminophen in water. Among all these prescriptions, acetaminophen was one of the active principles in three out of 15 main prescribed medications in Colombia in 2020 [3]. On the other hand, studies have shown that in therapeutic doses, around 5% of acetaminophen is excreted without modifications [4]. Therefore, acetaminophen ends up making its way to rivers and oceans affecting living organisms [5].

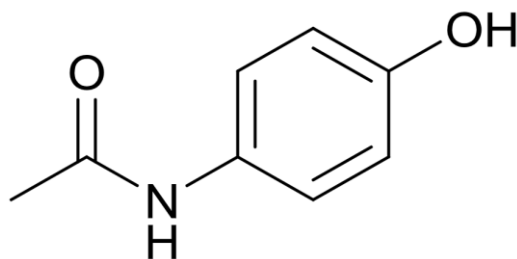


Figure 1. Molecule of acetaminophen [6]

Acetaminophen ($C_8H_9NO_2$, **Figure 1**) consists of a central benzene ring, with a hydroxyl group attached to one of the carbon atoms, and a nitrogen (containing group known as an amide) attached to another carbon atom. The molecule is stabilized by hydrogen bonding between the hydroxyl and amide groups. Acetaminophen can be identified through an electrochemical oxidation process resulting in N-acetyl-p-benzoquinoneimine (**Figure 2**). Therefore, electrochemical sensors, which are commonly used in analytical techniques in many different fields, can be used to detect acetaminophen. Typically, these sensors utilize a mesh of electrodes to measure the concentration of a chemical species in a sample by applying an electric signal and detecting the resulting current flow, which typically depends on the concentration of the aimed specimen (for this work acetaminophen). Electrochemical sensors are usually operated with established electrical techniques including voltametric methods which are often preferred when using these types of sensors due to advantages such as: high level of sensitivity, small sample volumes, and short analysis time [7]. Among the voltametric methods, cyclic voltammetry, which uses a triangular waveform to promote oxidation and reduction reactions, is widely used. The essential parameters in cyclic voltammetry are the peak-to-peak voltage and the signal frequency.

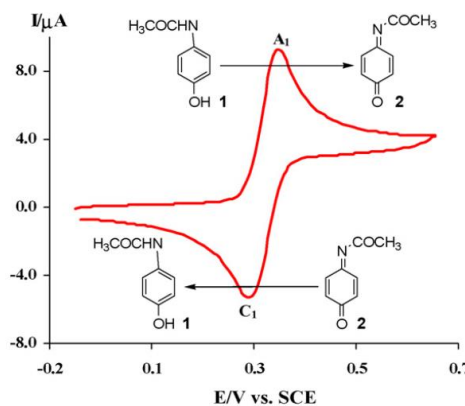


Figure 2. Cyclic voltammogram of 1mM acetaminophen at glassy carbon electrode, in ammonia buffer solution (pH=9.0) [8]

Different devices have implemented cyclic voltammetry for biosensing purposes. For example, smartphone-based devices have been developed to work using cyclic voltammetry in the detection of glucose [9]; portable biosensors using cyclic voltammetry for accurate nitrate determination [10]; low-cost multi-technique portable device for remote biosensors [11].

Inspired by some of these biosensing solutions, this work aims the development of portable sensing devices capable of measuring concentration of acetaminophen in water as an alternative to a complex laboratory infrastructure for the same purpose. Specifically, cyclic voltammetry can be combined with microfluidic systems for *in-situ* testing to enable such portable systems under the concept of *lab on a palm*. Monitoring of water quality can

be a first step to mitigate the impact of pharmaceutical pollutants like acetaminophen in water.

2. Objectives

2.1 General objective

Implement a standardizable design of an electrochemical sensor based on a microfluidic system and compatible with portable potentiostats to determine acetaminophen concentrations in water.

2.2 Specific objectives

- Design and manufacture the electrochemical sensor.
- Design and manufacture the coupling system for microfluidic systems.
- Characterize the sensor's response to various concentrations of acetaminophen in purified water in connection with a portable potentiostat.

3. Materials and Methods

3.1. Materials

The designs of the electrochemical sensor were made on the PCB design software "ALTIUM DESIGNER" version 22.11.1 (Altium Limited, Chatswood, New South Wales, Australia) and CAD design software "Shapr3D" version 5.270.4434.0 #77dcf552 (Shapr3D Zrt., Budapest, Hungary).

The manufacture process required: two acrylic sheets of $50\text{ cm} \times 35\text{ cm} \times 2\text{ mm}$ from *Comercial Papelera*, Bogotá, Colombia; TESA POWERBOND double-sided tape acquired from *Homecenter*, Bogotá, Colombia; TRUPER double sided mounting tape from *Ferreco*, Bogotá, Colombia; HR glue for acrylic surfaces (methylene chloride) from *Comercial Papelera*, Bogotá, Colombia; in-house developed functional device for microfluidic systems bonding [12]; SIHAO 80W laser cutting machine; 21 3mm screws from *Tornillos y Herramientas 777*, Bogotá, Colombia; 21 3mm nuts from *Tornillos y Herramientas 777*, Bogotá, Colombia; 9 $25\text{ mm} \times 75\text{ mm} \times 2\text{ mm}$ electrodes made of FR4 and copper with a tin cover fabricated at the printed circuits laboratory at *Universidad de los Andes*, Bogotá, Colombia; transparent adhesive vinyl from *Comercial Papelera*, Bogotá, Colombia; Cutting plotter Graphtech CE2800 from *Graphtech America Inc.*, California, United States; Xerex conductive silver ink from *Electrosena*, Bogotá, Colombia; DLAB MS-H280-Pro hot plate; hydrochloric acid (HCl) solution (0.1 M) from *Merck*, Darmstadt, Germany; kit mototool Dremel 3000 130W from *Homecenter*, Bogotá, Colombia; universal glue "PEGANTE PLUSS" from *Comercial Papelera*, Bogotá, Colombia.

The testing and electrochemical characterization process required: acetaminophen from *Tecnoquímicas*, Bogotá, Colombia; 8 FR8 silicon catheters from *Sherleg Laboratories S.A.S.*, Bogotá, Colombia; in-house developed portable potentiostat [11]; blue dye "Xilonte Azul 009" from *Roseta & Calidad... a todo color*, Funza, Colombia; 18 metallic coupling tubes; transparent acrylic nail polish from *Masglo*, Cerescos S.A.S., Bogotá, Colombia.

3.2. Electrode Design

The general design of the electrode used in [11] (**Figure 3**) was chosen for this project as its use was intended for the portable potentiostat.

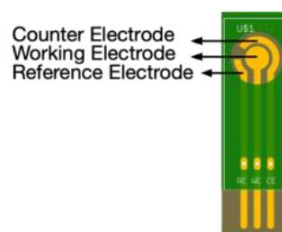


Figure 3. Three-electrode electrochemical cell [11]

3.2.1. Calculations

Having chosen the shape of the electrode, the three areas for the working electrode (A_1), counter electrode (A_2) and reference electrode (A_3) had to be calculated. These areas involved three radii: r_1 as the radius of the working electrode; r_2 as the inside radius of the counter and reference electrodes; r_3 as the external radius of the counter and reference electrodes. As shown in **Figure 4**, there were eight parameters to determine to achieve the desired shape for the electrodes. To reduce the free variables, the following restrictions were taken as design rules:

$$A_1 = A_2 \quad (1)$$

$$A_1 = 2 \cdot A_3 \quad (2)$$

$$r_2 - r_1 = 1.0 \text{ mm} \quad (3)$$

$$r_3 - r_2 = 2.0 \text{ mm} \quad (4)$$

Likewise, given the space availability r_3 was set to a value of 5.5 mm which resulted in $r_2 = 3.5$ mm and $r_1 = 2.5$ mm. With these values it was possible to find the three areas of interest (A_1, A_2, A_3). Finally, the angles for each of the arcs were obtained from the equations for A_2 and A_3 :

$$A_1 = A_2 = \pi r_1^2 \approx 19.6 \text{ mm}^2 \text{ and } A_3 = 0.5 \cdot A_1 \approx 9.8 \text{ mm}^2 \quad (5)$$

$$A_2 = 0.5 \cdot \phi_1 \cdot (r_3^2 - r_2^2) \text{ and } A_3 = 0.5 \cdot \phi_1 \cdot (r_3^2 - r_2^2) \quad (6)$$

$$\rightarrow \phi_1 = (2A_1)/(r_3^2 - r_2^2) \text{ and } \phi_2 = 0.5 \cdot \phi_1 \quad (7)$$

$$\phi_1 = 125.0^\circ \text{ and } \phi_2 = 62.5^\circ \quad (8)$$

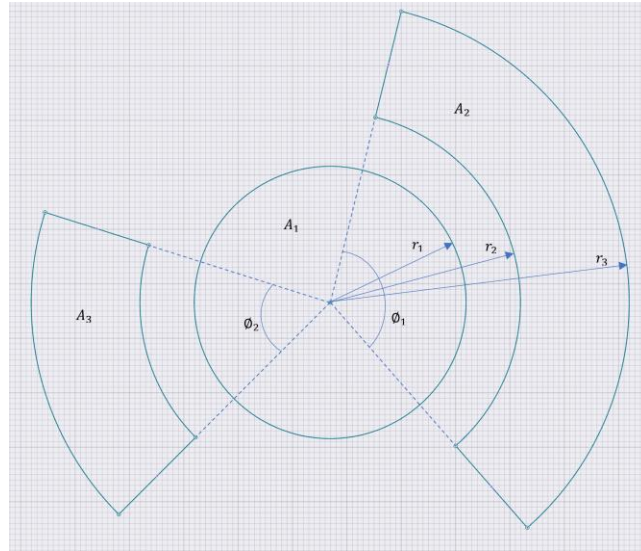


Figure 4. General shape design for the electrode; showing the eight parameters involved in the design.

3.2.2. Electrical design

With the geometric characteristics defined, the software Shapr3d (Windows and iPad OS versions) was used to draw the final shape of the electrode as well as render 3D models of the outcome. The 2D sketches were exported as .DWG files.

The .DWG files were then imported to Altium Designer and used as guidelines to create the different polygons needed to complete the three-probe electrode. This was accomplished through the command “Create Polygon from Selected Primitives” under the tab “Tools>Convert”. Finally, gerber files were generated and sent to the printed circuits laboratory at Universidad de los Andes.

3.3. Channel design

The software Shapr3d was also used to draw 2D sketches and render 3D versions of the channel for the samples. Keeping a minimum distance of 1 mm, a channel for the samples was design on one of the acrylic layers. The design embraces the whole electrode area and is meant to reduce turbulent flow. The second acrylic layer is meant to be the in and

out points for the samples and work as a connection point with microfluidic systems. Once the design was finalized the sketches were exported as .pdf files for the assembly process.

3.4. Assembly process

3.4.1. Acrylic system

One side of the acrylic sheet was covered with the TESA double-sided tape. Next, the two different layers were laser-cut into the acrylic resulting in eight pieces of each of the two layers. Using methacrylate and the device for microfluidic systems bonding [13], the two pieces were joined to each other. The parameters set for the device are shown in the **Table 1**. Then, methacrylate was applied to the outside and inside borders of the channel to minimize leak risks. Once the methacrylate dried, the first leak-test procedure took place; 12 acrylic pairs were glued together, and leak tested. Using the Mototool, the screw holes in the top acrylic layer were enlarged to ensure the screws could fit. The same process was repeated with the TRUPER double-sided tape.

Table 1. Parameters set for the microfluidic systems bonding device [13]

Parameter	Set value
Temperature [°C]	0 ¹
Weight [kg]	5
Time [minutes]	5

¹Value set for no heat generation.

3.4.2. DIY Antisolder

Two *DIY* techniques for antisolder were used: the first one involved applying acrylic nail polish on top of the PCB, leaving the electrode and soldering points uncovered, and curing the nail polish with an UV lamp; the second method involved cutting the anti-solder mask into adhesive vinyl with a cutting plotter machine and adhering the resulting shape on top of the PCB. Initially, these methods were implemented on two of the PCBs and then the acrylic was pasted to the PCBs and the screws were put in place. Afterwards, both systems were tested to evaluate any existence of leaks.

3.4.3. AgCl coating for the reference electrode

A silver chloride coating was applied to the reference electrodes of six of the PCBs (excluding the two PCBs used for the first test round with the antisolder techniques). First, the surfaces of the PCBs were cleaned using 70% ethanol. Then, the reference electrode was covered with conductive silver ink using a fine painting brush and was dried on a hotplate at 50°C for 15 minutes. Once the ink was dried, 5 µL of a solution of HCL 0.1 M were put on each of the reference electrodes preventing the drops from entering in contact with the other electrodes to avoid corrosion. The HCL solution was left for 30 minutes at room temperature. Finally, the electrodes were washed using purified water.

3.4.4. Final coupling stage

The coupling tubes were glued to the top side of the acrylic and dried for 3 hours. The channels formed by the acrylics were cleaned using 70% ethanol as well as the surfaces of the electrodes. Then the electrodes and the acrylic were bonded through the TRUPER double-sided mounting tape and the screws. The latter were tightened using pliers to turn the nuts clockwise. Finally, 3 × 1 pin-headers were soldered to the PCB.

3.5. Leak test procedures

Two leak tests took place: first one to ensure the acrylic was fully sealed and a second one to ensure the whole system including the PCB was sealed.

3.5.1. Acrylic test

Five drops of blue dye were added to 100 mL of purified water. As seen on **Figure 5**, a 5 – mL syringe was used to add the colored water to the channels. The acrylics were placed on paper towels and left for 10 minutes. Afterwards, the paper towels were checked for any water that could have leaked through the acrylic.

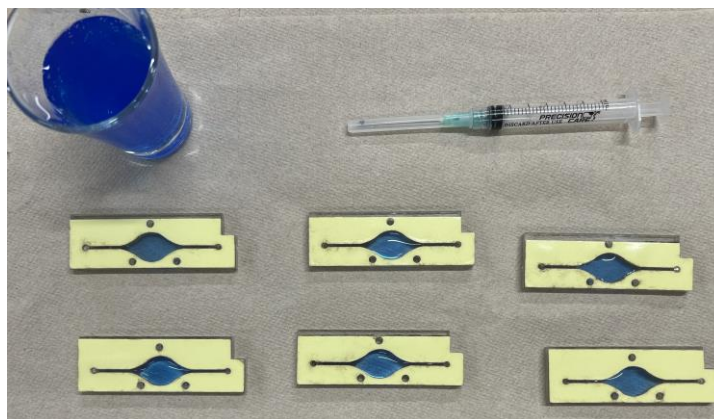


Figure 5. Setup for leak tests on the acrylic structures

3.5.2. System test

Once the whole system was put together, the final leak test consisted of using the colored water and pumping it through the systems with the aid of a 10 mL syringe and two silicon catheters (**Figure 6**). Once the systems were filled, they were left with the water for 5 minutes and then checked for leaks around the channel, coupling tubes and borders of the PCBs. Systems using TESA and TRUPER double sided tape and vinyl and acrylic as antisolder layers were tested to find any leaks.

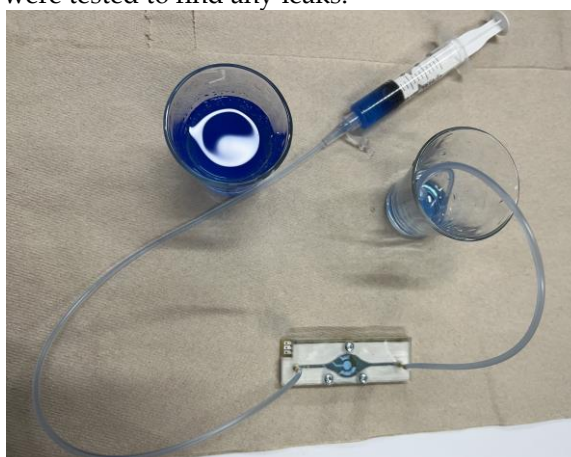


Figure 6. Setup for leak tests on the ensembled systems

3.6. Acetaminophen dissolutions

Nine dissolutions of acetaminophen (**Table 2**) were prepared from a stock solution of 600 mg/L with a pH between 6.0 and 6.5. For each dissolution a sample of the stock was mixed with enough purified water so the nine dissolutions would have a volume of 30 mL.

Table 2. Concentrations of prepared acetaminophen dissolutions

Concentrations	[mg/L]	[mM]
C0	0	0
C1	5	0.0331
C2	10	0.0662
C3	25	0.1654
C4	50	0.3308
C5	100	0.6615
C6	150	0.9923
C7	200	1.3231

C8	250	1.6538
C9	300	1.9846

3.7. Electrochemical sensor characterization

The characterization with the acetaminophen dissolutions was made through the set up shown in **Figure 7**. Using the 5 mL syringe and two silicon catheters for each sensor, enough liquid was pumped through the systems to cover the whole electrode's surface. In between samples, purified water was pumped through the channels to clean them, and the system was purged so the next sample could be pumped through. Using a portable potentiostat [11], cyclic voltammetry tests were run; the parameters used are shown in **Table 3**. For each concentration, the tests were run three times on the four sensor systems.

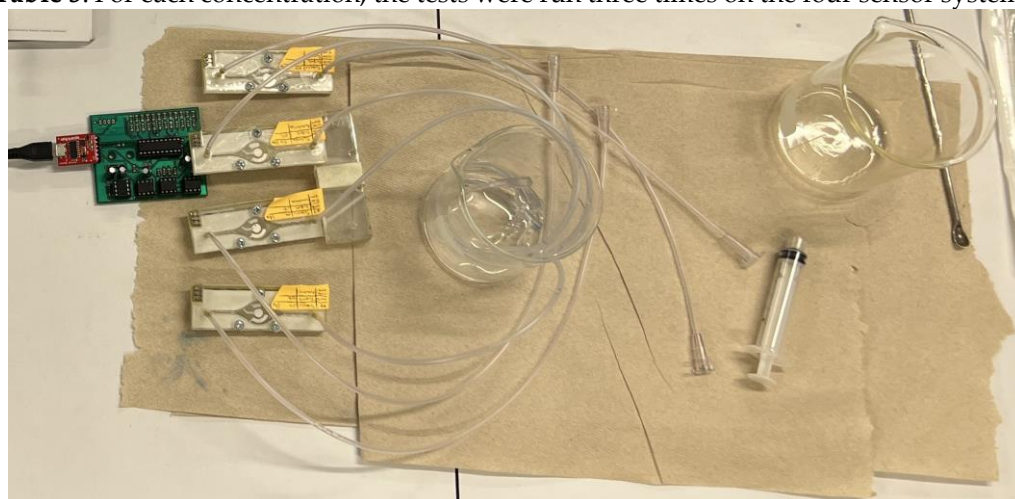


Figure 7. Electrochemical characterization setup

Table 3. Parameters used with the portable potentiostat [11]

Parameter	Value
Start point [V]	0.000
First vertex [V]	0.800
Second vertex [V]	-0.400
Zero crosses	6
Scan rate [V/s]	0.050

4. Results

4.1. Designs

4.1.1. Electrode design

The use of the CAD software Shapr3D yielded electrodes designs (**Figure 8**) that could be rapidly edited and exported to ALTIUM DESIGNER (**Figure 9**) to generate necessary files to manufacture PCB's. Shapr3D facilitated the implementation of rounded designs that might not be convenient to draw in the Altium environment.

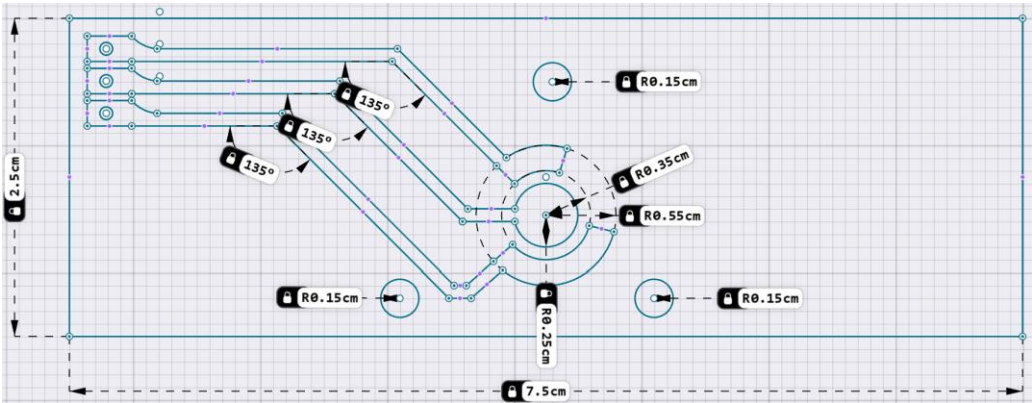


Figure 8. Shapr3D electrode design

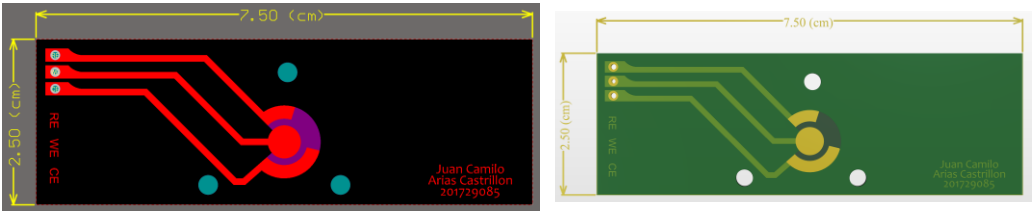


Figure 9. ALTIUM DESIGNER PCB's design

4.1.2. Channel design

Shapr3D permitted a flawless integration of the electrode's design with the channel design (Figure 10).

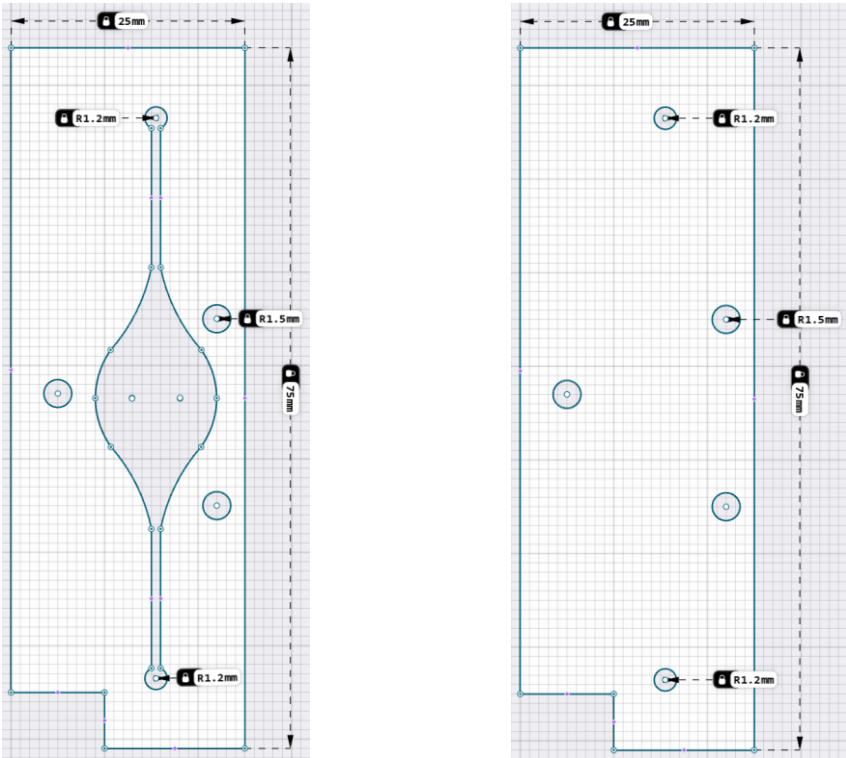


Figure 10. Channel design in Shapr3D

4.1.3 Assembled System

The assembled system was attained by using adhesive vinyl as antisolder and TRUPER double-sided tape to bond the PCB with the acrylic as shown in **Figure 11**.



Figure 11. Shapr3D's 3D render next to the final assembled system

4.2. Systems physical tests results

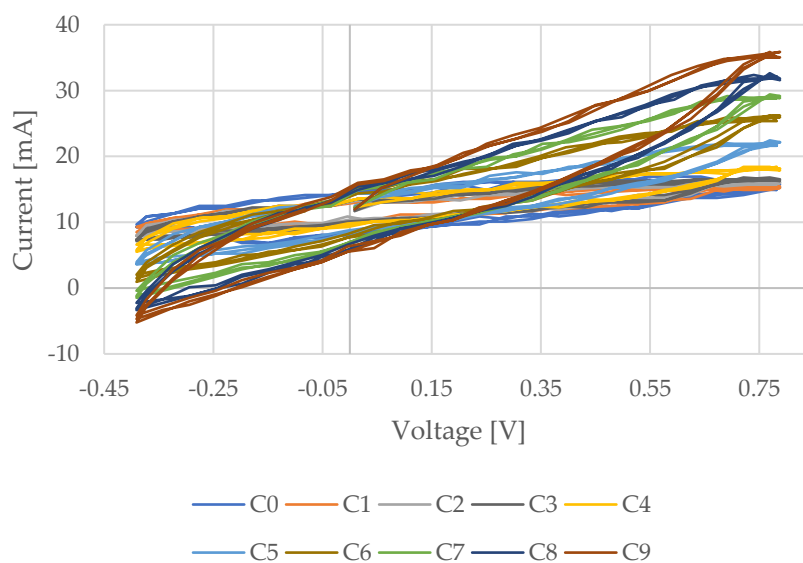
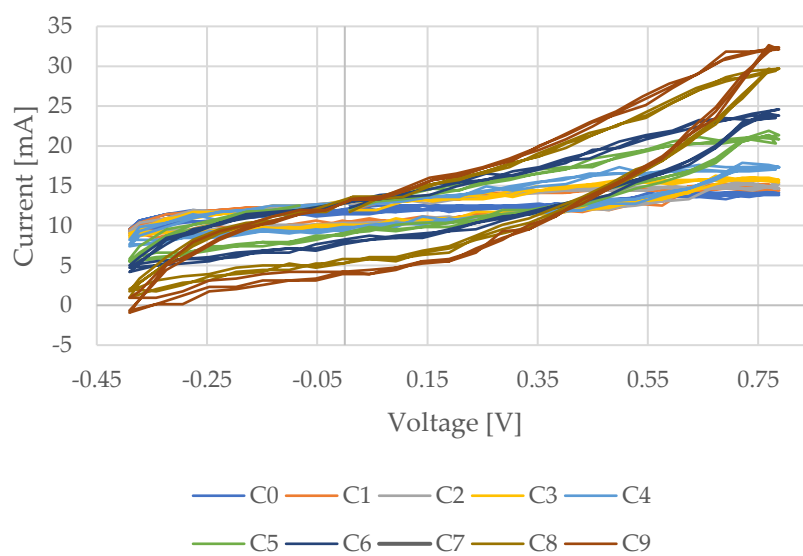
From the tests performed during and after the assembly process, it is showed that:

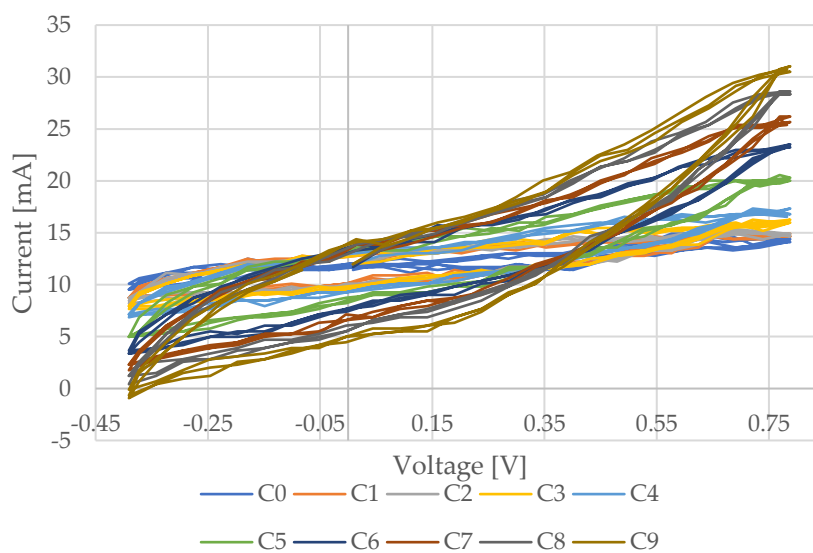
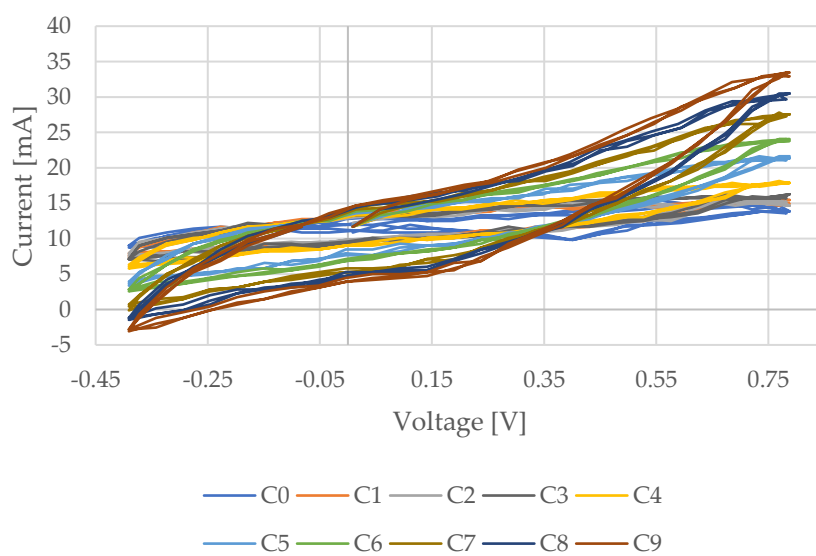
- The TESA POWERBOND double sided tape is not fit for sealing channels with a width greater than 2.5 mm. The gaps between each strip of the tape turned in micro-channels that enabled leaks.
- Using acrylic nail polish is not suitable as the final antisolder surface will be uneven and give way to leaks.
- The adhesive vinyl as an antisolder mask provided an even surface to seal the channel in combination with the TRUPER double sided mounting tape.

4.3. Electrochemical characterization results

For each concentration a voltammogram from -0.4 V to 0.8 V was obtained per electrode (**Figure 12-Figure 15**). The voltammograms permitted to determine a dead zone of the electrodes based off the readings for concentration C1 through C3. For each concentration, the average peak current was obtained by finding the peak current out of the three cycles ran and averaged between the three replicas. The average peak current was used to determine each sensor's characteristic curve through linear regression (**Figure 16-Figure 19**). These results permitted to determine the sensor's maximum resolution and sensibility (**Table 4**).

The average currents between each concentration's replica (excluding C0 through C3) were used to determine the oxidation voltage of the acetaminophen in an aqueous solution with a pH between 6.0 and 6.5 (**Table 5**). This voltage was obtained by finding all the instances of peak current for each of the five concentrations (C4 through C9) and averaging the corresponding voltages.

**Figure 12.** Voltammograms results for electrode 5**Figure 13.** Voltammograms results for electrode 6

**Figure 14.** Voltammograms results for electrode 7**Figure 15.** Voltammograms results for electrode 8

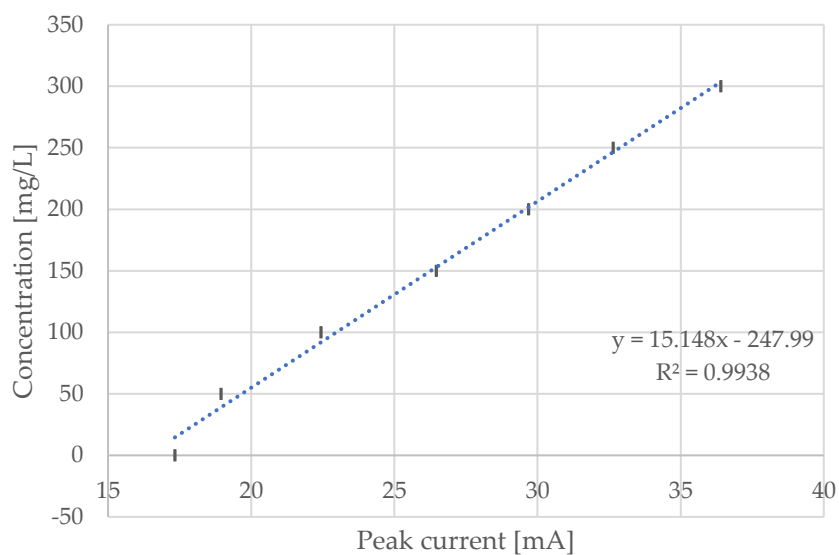


Figure 16. Electrode 5's characteristic curve through linear regression

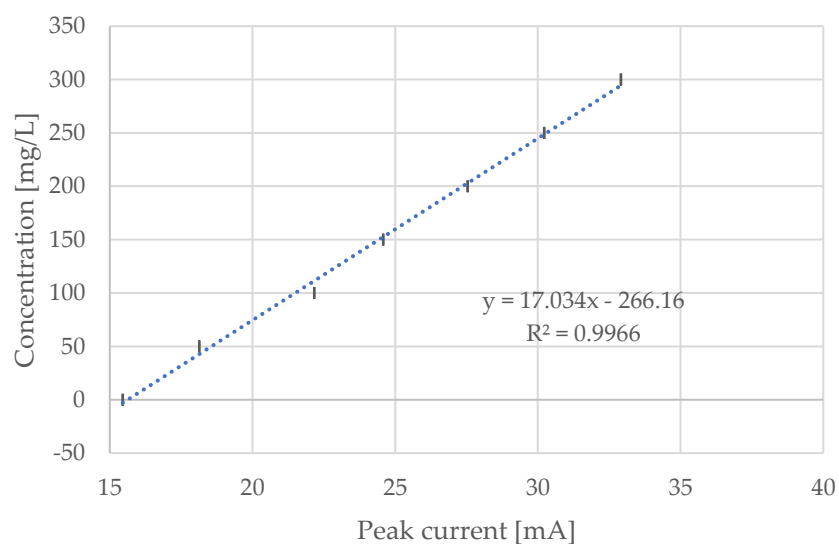


Figure 17. Electrode 6's characteristic curve through linear regression

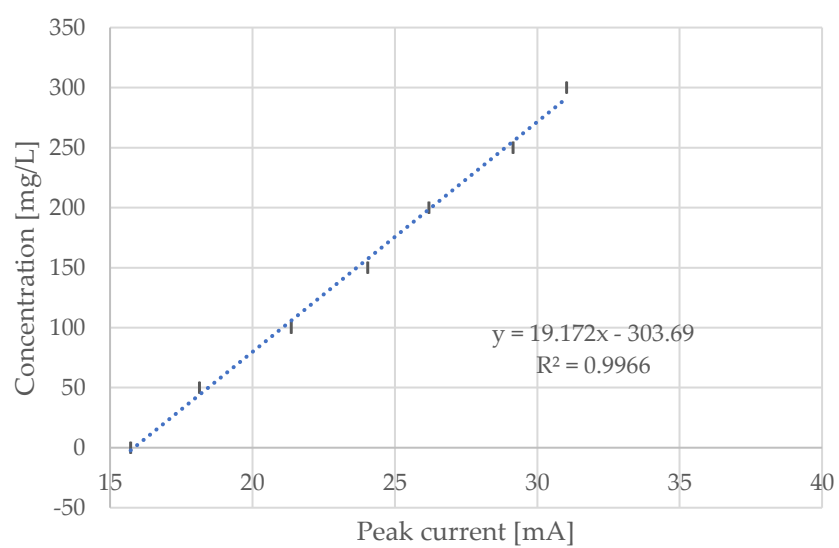


Figure 18. Electrode 7's characteristic curve through linear regression

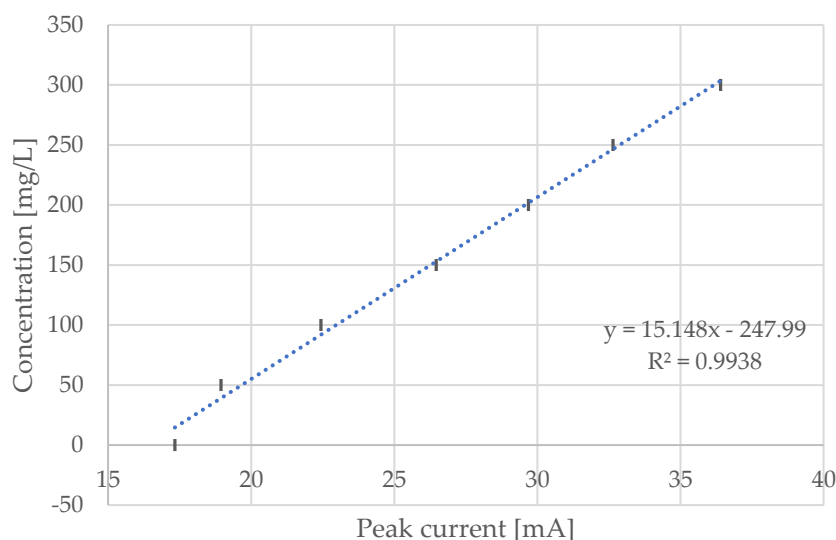


Figure 19. Electrode 7's characteristic curve through linear regression

Table 4. Electrochemical sensor's measure capabilities based on the characterization performed

Sensor	Sensitivity [$mg\ L^{-1}/mA$]	Linear range [mg/L]	Detection limit [mg/L]	Error Percentage ¹
Electrode 5	15.148	50-300	50	1.999%
Electrode 6	17.034			1.145%
Electrode 7	19.172			1.195%
Electrode 8	15.148			1.999%

¹Maximum and minimum average difference

Table 5. Average oxidation voltage of acetaminophen in aqueous solutions with pH between 6.0 and 6.5 determined through the electrochemical device

Sensor	Average oxidation voltage [V]	Precision
Electrode 5	0.770	91.311%
Electrode 6	0.771	91.323%
Electrode 7	0.775	91.367%
Electrode 8	0.775	93.038%

5. Discussion

The implemented design for the electrochemical sensor (**Figure 8-Figure 11**) is consistent with previous literature [13]–[17] in which the aim is to expose the electrodes directly to the samples by using the PCB as part of the structure of the channels. The physical tests highlighted the importance of including different leak test's stages throughout the assembly process.

The electrochemical characterization (**Figure 16-Figure 19**) showed the capabilities of the designed electrode to measure concentrations of acetaminophen in purified water between 50 – 300 mg/L. The sensor's response to cyclic voltammetry (**Figure 12-Figure 15**) was like that of the tested sensors in the development of a portable electrochemical device [11] which included the potentiostat used in this project. As seen in [11], a better response from the sensor could be obtained using modified electrodes such as those with laccase immobilization techniques. This is also seen in previous research [13] as well as in literature comparing different electrodes and techniques used to determine acetaminophen concentration [6].

Taking advantage of the versatility in the design process of both the electrode and the acrylic channel further developments should aim to reduce the electrodes diameter, the channel width and reduce the acrylic layers to one. As mentioned before, it would be recommended to implement functionalization techniques including biomolecules capable of catalyze redox reactions.

6. Conclusions

This project developed an electrochemical sensor compatible with portable devices.

- On the one hand, this project was able to establish a standardizable design process for electrochemical sensors that couple with microfluidic systems.
- There was a proportional relation observed between the peak current in each voltammogram and the concentration of acetaminophen. The device was able to differentiate samples with concentrations ranging from 0 mg/L to 300 mg/L with increasing steps of 50 mg/L. The average error in the measures taken was less than 2% throughout the four electrochemical systems that were assembled. The measured peaked current allowed to determine the oxidation voltage of the aqueous solutions of acetaminophen with a pH between 6.0 and 6.5.
- The developed process is standardizable and allows for a relatively fast assembly stage once the printed circuits are ready. The multiplatform origin of these PCB's grants a high flexibility degree in terms of changes, flaw corrections and scalability. The materials and tools required (excluding those of the PCB's) are commercially accessible and allow for ease of replication.

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