

## Referees Responds

### Referee #1

**(1) The text must be standardized, in situ, sat., vs. or italics or not, check significant figures, Tables: some should be moved to the appendix, Figures to be improved, such as the respective caption.**

Thanks for the comment. The text was standardized according to the recommendations. Thus, in situ was used. The italics were removed, and the abbreviations were checked throughout the thesis. Tables were gathered into the supplementary information, and it only included Tables which summarize the most important information (e.g., the ANOVA test in Chapters 3.1 and 3.2, inhibition efficiency in the case of chapter 3.2, and the comparison table in chapter 3.3). The resolution and information in the figure were revised and corrected throughout the text, and the captions were better written to be more explicative.

**(2) As I said during the thesis presentation, the introduction part should cover the 3 themes of the thesis and not about the common electrochemical and other techniques, that should appear in annex. And that's why some parts are repeated.**

Thanks for the comments. The introduction was rewritten. In the current status, it gathered and explained information about the three main chapters of the research: (i) drug delivery systems (DDS), (ii) corrosion protection, and (iii) chemically modified electrodes to sense sodium diclofenac salt. The techniques such as cyclic voltammetry, square wave, and so on were removed to avoid repetition. Now, there is not any redundant information either in the introduction or in the literature review.

**(3) This study is a model study. As there was no state of the art, I don't know which drugs would be interesting to administer in saliva. I think that paracetamol does not need any support and there are many drugs that are already administered under the tongue (such as for the heart). Why delivery of PA with a support? What is the objective of this study? In my opinion, this part should be reworded in relation to the objectives. The work is interesting. In the paper Materials Today Communications, everything is more organized, including the figures.**

Thanks for the comments. Section 2.1.5 includes the state of the art about DDS in connection with Paracetamol (PA) delivery. Moreover, the necessity of producing a DDS

over the Ti alloy can be explained according to the following:(a) PA is among the most consumed analgesic antipyretic drugs. But they release faces some problems such as fast release and absorption, which decrease their efficiency and increase the necessity of higher drug loads, which can produce side effects. Thus, it is necessary to investigate more efficient DDS; (b) Ti-alloys are one of the most used alloys in the production of medical devices (e.g., dental implants, prostheses). So, to coat them with polymers loaded with analgesic drugs (in our case PA) increases the efficiency of the therapeutical treatment and the patient mood and protects the implant against destruction caused by the direct interaction with the environment (in our case saliva); (c) it is necessary to evaluate alternative methods to investigate the drug release and apply these methods in online measurements. This can be solved using electrochemical impedance spectroscopy, which is a non-destructive method. This preserves the characteristics of the implant while giving accurate information about the release concentration of the PA. Finally, chapter 3.1 was reorganized to be more informative and organized, as is reported in the paper published in material today communication (J. Hidalgo Viteri, N. Cotolan, Lucian Barbu-Tudoran, G.L. Turdean, A paracetamol-poly(3,4-ethylenedioxythiophene) composite film for drug release studies, Mater. Today. Comm. 34 (2023) 105084, <https://doi.org/10.1016/j.mtcomm.2022.105084>).

#### **(4) Magnification in SEM images**

Thanks for the comment. The magnification of the SEM images was included in all the three chapters. They are described in the label of Figure 4 (Section 3.1), Figure 17 (section 3.2), and Figures 25,26 and 27 (section 3.3).

#### **(5) Drug Delivery systems, corrosion, electrodes modification State of art: Compare it with what has already been done and what your contribution is.**

Thanks for the comment. The current state of art regarding DDS, corrosion, and chemically modified electrodes was included in sections 2.1.2.3, 2.2.4.2.1, and 2.3.5.2, respectively. And the results were compared with the ones obtained during the experimental stage of the thesis dissertation.

#### **(6) Ti is the support electrode. What role would Ti play in real applications for paracetamol??**

Thanks for the comment. Point (3) indicates that Ti is one of the most commonly used materials in medical applications. Thus, coating the alloys with a DDS loaded with PA increases the therapeutic effect and the patient mood (reducing the frequency of PA administration) and increases the lifetime application of the Ti alloys exposed to human fluids (in our case, saliva).

**(7) The graphic (Figure 14) is of very poor quality. Can it be improved? AND TO EXPLAIN IT BETTER**

Thanks for the comment. The quality of Figure 14 (Figure 10 in the corrected version) was improved and the explanation both in the labeling and in the text were explained better. Now, it highlights the principal findings and how this figure demonstrated the crosslinking between the polymethyl methacrylate (PMMA) and the ibuprofen (IBU).

**(8) Fig. Figure, figure ??: standardize everything**

Thanks for the comment. The term Figure was chosen to describe the figures throughout the text.

**(9) In my opinion, in this study, with so much comparative data, a statistical comparison (ANOVA) should have been performed. In other words, the results obtained are significantly different or not.**

Thanks for the comment. An ANOVA test was included in chapters 3.2 and 3.3 to study if there is a significant difference between the experiments. Thus, there was a significant difference ( $p < 0.01$ ) between the IBU and PMMA (see Table 6) when the efficiency in the corrosion protection was evaluated. Furthermore, there was a significant difference ( $p < 0.01$ ) between the type of extraction technique and the type of plant in relation to the corrosion protection (see section 3.2.4.7.1.). Moreover, there was a significant difference ( $p < 0.01$ ) between the different nanomaterials used in the production of chemically modified electrodes, taking into consideration the limit of detection (LOD) as stated in section 3.3.6.9.4. Overall, the ANOVA test allowed us to analyze if the prepared technologies differ from each other under the same investigations (protection efficiency in the case of chapter 3.2, and analytical performance of the devices in the case of chapter 3.3).

**(10) Scientific notation:  $1.51 \times 10^{-2} \pm 0.21$ . This applies to all numbers written in scientific notation.**

Thanks for the comments. Scientific notation was kept all over the text. The significant digits were kept at 2.

**(11) Title: ELECTROCHEMICAL TECHNIQUES APPLIED TO THE ENVIRONMENT PROTECTION AND HEALTH?**

Thanks for the comment. The title of the dissertation was changed to “ELECTROCHEMICAL TECHNIQUES OF INVESTIGATIONS—A TOOL FOR DIFFERENT APPLICATIONS” to amplify its spectra. Thus, the title encompasses three chapters and extends beyond the environment. Now, it involves the medical field (DDS), industrial field (corrosion protection), and environmental field (electrochemical devices to detect DS in wastewater).

**(12) FOR HPLC/MS/MS no mention is made of the sample pre-treatment that is required, usually solid phase extraction**

Thanks for the comment. The UPLC-MS/MS method used during the experimental part was not included in the text because the results were not published yet and we wanted to avoid any type of plagiarism. However, the procedure can be found on our last published paper (Juan Hidalgo, Graziella Liana Turdean, Luigi Falciola, Valentina Pifferi, Ildiko Galambos, Hajnalka Jankovics, Eva Toth, Luis Hidalgo, A functionalized multiwalled carbon nanotubes decorated with an engineered flagellin protein as a modified electrode for the detection of diclofenac sodium, *Microchem. J.* 216 (2025) 114698, <https://doi.org/10.1016/j.microc.2025.114698>). Therefore, a brief explanation is as follows:

(a) collection of the wastewater samples by following the U.S. Environmental Protection Agency (EPA) standard Operating Procedure (EPA-LSASDPROC-306-R6 (Wastewater Sampling (306) AF. R3)); (b) wastewater samples were diluted and they were spiked with an isotopically labelled internal standard mix (Citalopram-D6, Carbamazepine-D10, Alprazolam-D5); (c) these samples were extracted using automated solid-phase extraction equipment; (d) the extracted samples were dried and reconstituted; (e) injection of the samples in the UPLC-MS/MS machine.

**(13) PA gives 2 peaks, or a multi-component peak**

Thanks for the comment. Paracetamol gave a single peak as it is indicated in Figure 8A, and it is in accordance with other studies reported in the literature.

**(14) Very long sentences, paragraphs (such as page 86)**

Thanks for the comments. The paragraphs were rewritten to have a shorter length and to be more informative.

**(15) If the first results with this Tara\_ME extract were not promising, it made sense to continue with the following experiments? (page 134)**

Thanks for the comments. You are right; the results were not promising on page 134. However, confirming the results using electrochemical analysis methods was necessary. Moreover, it was necessary to continue the studies because further studies with other plants were carried out (e.g. Guayusa). Therefore, it was important to discuss why maceration extraction should not be used with this plant.

**(16) Dots should appear in graphs instead of commas**

Thanks for the comments. Most of the graphs were changed to show points instead of commas. However, some figures still contain commas due to software incompatibility.