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Measurement of Paracetamol Concentration Using an Erbium-Doped Fiber Ring Cavity

Liliana Soares [1,2], Rosa Ana Pérez-Herrera [3,4], Susana Novais [1], António Ferreira [5,6,*], Susana Silva [1] and Orlando Frazão [1]

1 INESC TEC—Institute for Systems and Computer Engineering, Technology and Science, Rua do Campo Alegre 687, 4150-179 Porto, Portugal
2 Department of Engineering Physics, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal
3 Department of Electrical, Electronic and Communication Engineering, Public University of Navarra, 31006 Pamplona, Spain
4 Institute of Smart Cities (ISC), Public University of Navarra, 31006 Pamplona, Spain
5 LEPABE—Laboratory for Process Engineering, Environment, Biotechnology and Energy, Department of Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal
6 ALiCE—Associate Laboratory in Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal
* Correspondence: antonio@fe.up.pt

Abstract: Process Analytical Technology (PAT) has been increasingly used in the pharmaceutical industry to monitor essential parameters in real-time during pharmaceutical processes. The concentration of Active Pharmaceutical Ingredients (APIs), such as paracetamol, is one of these parameters, and controlling its variations allows for optimization of the production process. In this study, a refractometric sensor, implemented by an interrogation system based on an Erbium-Doped Fiber Ring Cavity (EDFRC), was presented and experimentally demonstrated. The Cavity Ring proposed included a 1×3 coupler. One port of the coupler was used to increase the optical power of the system through a Fiber Bragg Grating (FBG), and the other two ports were used as sensing head and reference. The sensor detected variations of paracetamol concentration with a sensitivity of $[(-1.00 \pm 0.05) \times 10^{-3}]$ nW/(g/kg) and a resolution of 5.53 g/kg. The results demonstrate the potential of this technology as a possible non-invasive PAT tool.

Keywords: process analytical technology; concentration; paracetamol; ring cavity; erbium-doped fiber

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1. Introduction

The pharmaceutical industry has widely used Process Analytical Technology (PAT) to monitor the process in real-time, allowing for a better understanding of the processes and improving the final product quality [1,2].

The PAT implementation requires sensors to measure the variables of interest, such as reagent or product concentration. For more than a century, the concentration measurement has been very important in the processing industries, including the pharmaceutical industry. Quick and accurate control of this parameter is essential to optimize production [1–3]. Controlling the concentration allows for cost reduction, waste production decreases, and maximization of reagents use [4].

In the pharmaceutical field, quantitative testing of Active Pharmaceutical Ingredients (APIs) is very common. For that, real-time API concentration measurements are desirable, as they avoid the sampling process. In this way, sample preparation is unnecessary, eliminating the possibility of time delays. However, sometimes the available PAT is destructive, time-consuming, and costly. For this reason, there is a continuous need to

develop new technologies that allow real-time measurements with high acquisition rates in a non-invasive/non-destructive way [4–7].

In this work, a refractometric sensor is proposed that is sensitive to the variations of paracetamol concentration—the case study. The implementation of the sensor was performed using an interrogation system based on a Cavity Ring design with a 1 × 3 coupler. One of the coupler ports was used as a sensing head (refractometric sensor), another as a reference, and the last one as a reflector filter to increase the optical power of the system by means of a Fiber Bragg Grating (FBG). The technology proposed can be used to monitor the variations of liquid API concentrations in real-time and in a non-invasive way.

2. Materials and Methods

This work proposed an Erbium-Doped Fiber Ring Cavity (EDFRC) for measurements of concentration in paracetamol liquid solutions. The experimental setup used is shown in Figure 1.

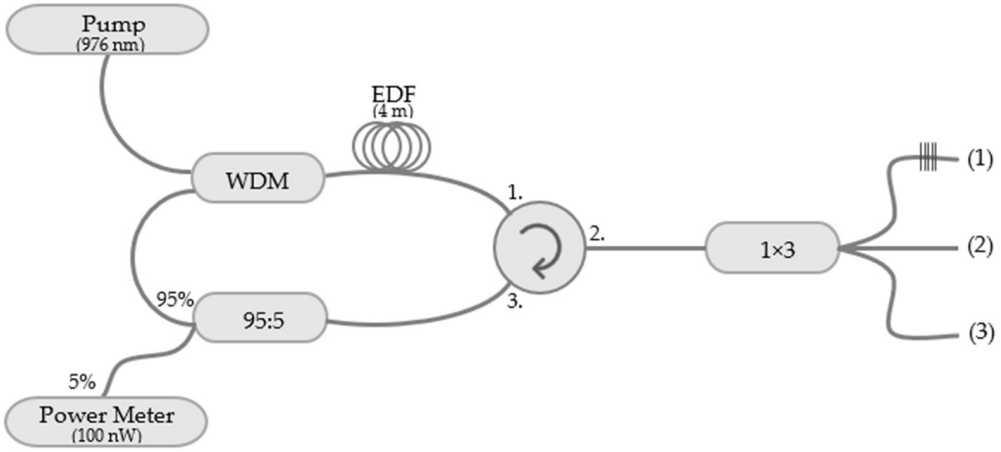

Figure 1. Experimental setup of the EDFRC proposed for paracetamol concentration measurements. Coupler output ports: (1) FBG; (2) reference and (3) sensing head.

A 980/1550 nm Wavelength Division Multiplexer (WDM) was responsible for injecting pump power into the EDFRC (976 nm), and the laser diode was temperature-controlled to ensure the stability of the laser output. The gain medium used consisted of 4 m of highly Erbium-doped fiber (EDF) with an active absorption coefficient of 5.0–6.7 dB/m @1531 nm. The EDF was connected to the common port of the WDM and to a 3-port optical circulator, which, in turn, was connected to a 1 × 3 optical coupler by means of port 2. Port 1 of the optical coupler was connected to an FBG, centered at 1543.65 nm; port 2 was used as a reference and port 3 was used as a sensing head.

The grating used corresponded to a commercial single FBG, centered at 1543.65 nm, with a reflectivity of 97.59% and a bandwidth of 0.243 nm at −3 dB.

For the acquisition of the optical response, a 95:5 optical coupler was used to extract 5% of the signal from the EDFRC to a power meter (see Figure 1). The use of the power meter allowed us to significantly reduce the power fluctuations associated with the influence of external factors, such as variations of pump power or room temperature.

Furthermore, the use of optical circulators in this configuration allowed us to avoid spatial hole-burning (SHB) because the unidirectional operation was guaranteed.

The fiber tips of the three output ports of the optical coupler were properly cleaved to ensure the Fresnel reflection. In the case of the fiber tip where the FBG was located, it was cleaved at 2 cm after the FBG.

The sensing head structure of this experiment is shown in Figure 2.

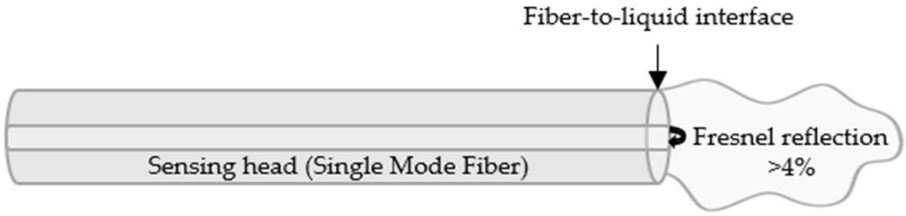

Figure 2. Scheme of the sensing head operating mechanism.

The physical principle related to the sensing head operating mechanism relies on measurand-induced intensity variation of the Fresnel reflection at the fiber-to-liquid interface monitored. Upon reaching the surroundings, the light is partially reflected. In this way, the measurement of refractive index variations is achieved with the intensity changes of the reflected optical signal. In this experiment, the ratio between the reflected light in the fiber-to-liquid interface and the incident light (Reflectance, R) can be estimated through the Fresnel equation for a reflection at a normal incidence, i.e., when the incident angle is equal to 0 [8]:

$$R = \left(\frac{n_t - n_i}{n_t + n_i}\right)^2 \quad (1)$$

where n_i corresponds to the refractive index of the fiber optic core (n_i = 1.468 RIU) and n_t corresponds to the refractive index of paracetamol liquid solutions (n_t > 1 RIU). According to Equation (1), less than 4% of the light guided by the fiber is reflected at the fiber-to-liquid interface monitored.

The concentration measurements were performed using eight standard liquid solutions of paracetamol (CAS number 103-90-02, min. 99% purity, supplied by Sigma-Aldrich) in a mixture of 40% (v/v) ethanol/deionized water, prepared at room temperature (~20 °C). The concentration of the solutions ranged from 52.61 to 219.25 g paracetamol/kg solvent, which corresponded to a refractive index range of 1.3637 RIU to 1.3899 RIU. To determine the refractive index of said solutions, an Abbe refractometer (ATAGO, DR-A1) was used to measure the samples. As expected, with the increase in paracetamol in solution, the samples become optically denser and, consequently, the refractive index linearly increased—Figure 3.

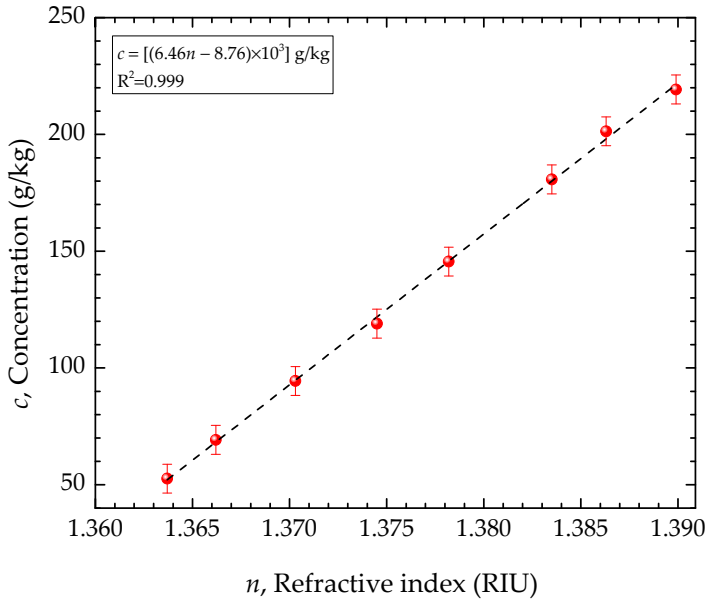

Figure 3. Concentration of paracetamol in solution as a function of refractive index. Measurements of refractive index performed using an Abbe refractometer.

Firstly, we performed a refractive index characterization of the solvent used in the paracetamol standard solutions: a mixture of 40% ethanol and 60% deionized water. The main objective was verified, and the output power was obtained for a reference refractive index, considering the solvent used in the paracetamol solutions. For this, mixtures of ethanol and deionized water with different percentages in volume were prepared.

The samples were measured using the Abbe refractometer, and we obtained a refractive index range of 1.337 RIU to, approximately, 1.357 RIU.

Using the experimental setup (Figure 1) for the mixture of interest (40% ethanol and 60% of deionized water), we obtained an output power of 15.57 nW for a refractive index of 1.352 RIU—Figure 4.

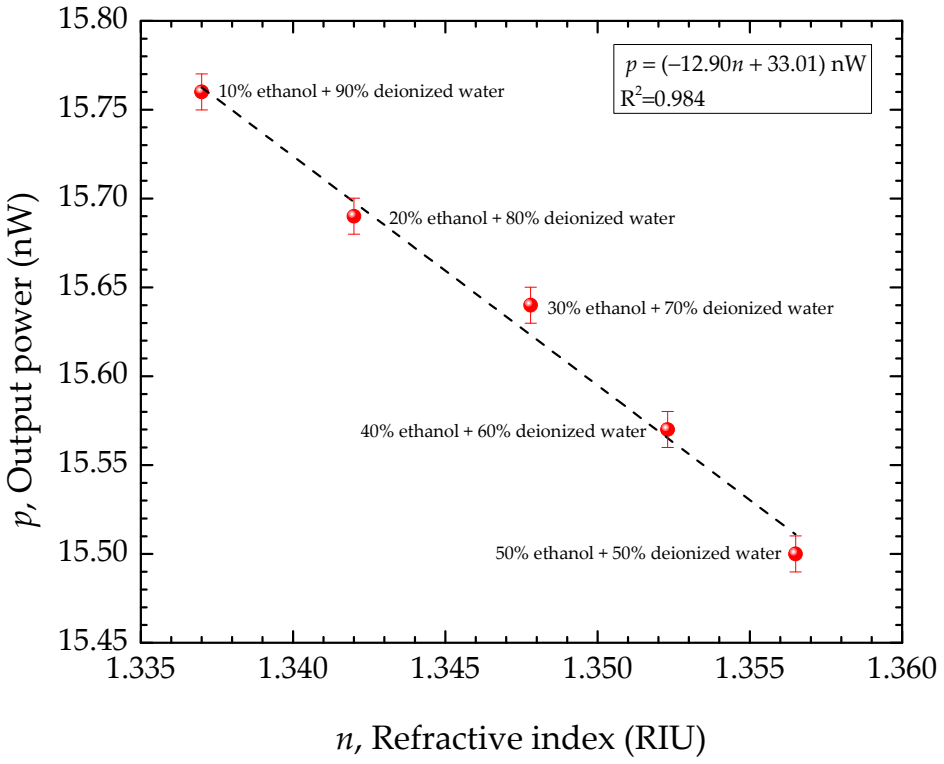

Figure 4. Refractive index characterization of the ethanol and deionized water mixtures. Measurements of refractive index performed using an Abbe refractometer.

3. Results and Discussion

3.1. Output Spectrum

The output spectra of the EDFRC were obtained using the OSA (YOKOGAWA, AQ6370D). They are shown in Figure 5 for the cases where: (1) the reference and the sensing head were placed in air (red line), and (2) the reference was immersed in the reference medium and the sensing head was placed in air (black line). It is important to refer to the fact that the reference medium used corresponds to a mixture of 40% ethanol and 60% deionized water (the solvent present in the paracetamol samples). In both cases, the configuration was pumped with 20 mW at 976 nm. The laser condition was not reached, as predicted, due to the low level of pump power. On the other hand, the ring configuration allowed for the spontaneous emission condition.

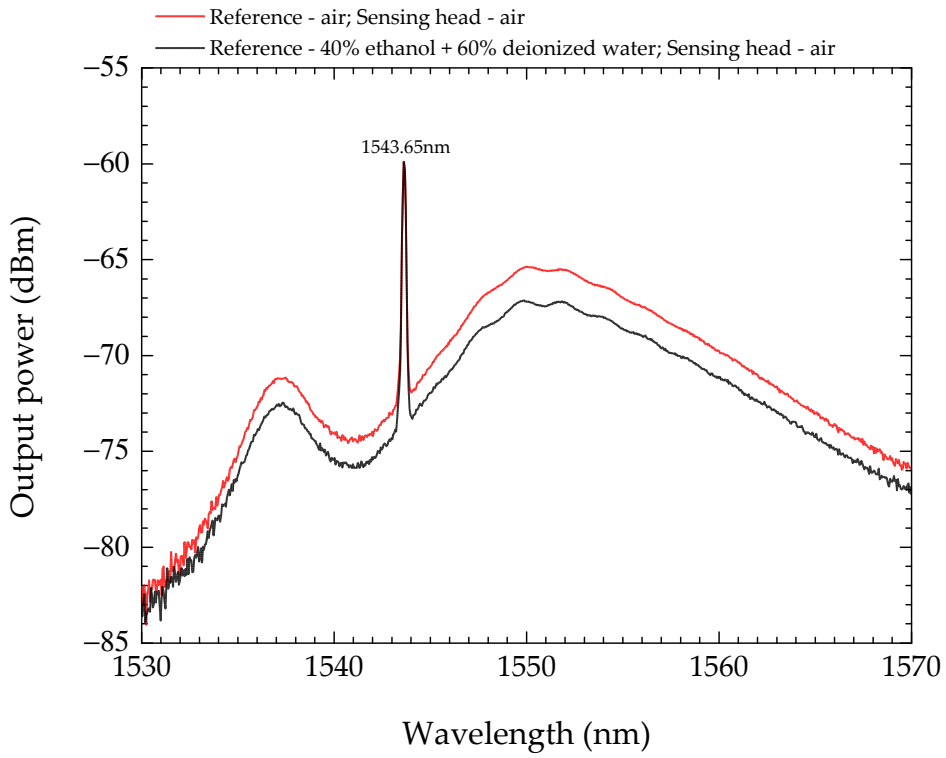

Figure 5. EDFRC output spectra pumped by a 976 nm laser at 20 mW when both reference port and sensing head were in air (red line) and reference port was in the reference solution and sensing head was in air (black line).

As can be seen in Figure 5, there is an output power level (~−60 dBm) centered at 1543.65 nm and an Optical Signal to Noise Ratio (OSNR) as low as 10 dB in both spectra. Furthermore, as expected, the output power level of the spectrum shown in red is higher than the one presented in black. The refractive index of the reference solution (1.352 RIU; black line) is higher than the refractive index of the air (~1.000 RIU; red line), which causes the referred optical power loss. In this way, the increase in the refractive index promotes the reduction in the amplitude of the reflected wave in the interface created by the fiber and the air/reference medium, generating the loss in optical power. The following measurements were performed by maintaining port 2 of the optical coupler (reference) in the reference medium of 40% ethanol and 60% deionized water.

3.2. Paracetamol Concentration Measurements and Sensor Sensitivity

The liquid samples of paracetamol were measured at room temperature using the experimental setup proposed in Figure 1. For that, the sensing head (port 3 of the optical coupler) was vertically immersed in each sample. The output power level in each measurement, obtained using the power meter (Agilent 8163B), is represented in Figure 6. A linear dependence between the output power and the paracetamol concentration was obtained (correlation factor of 0.995).

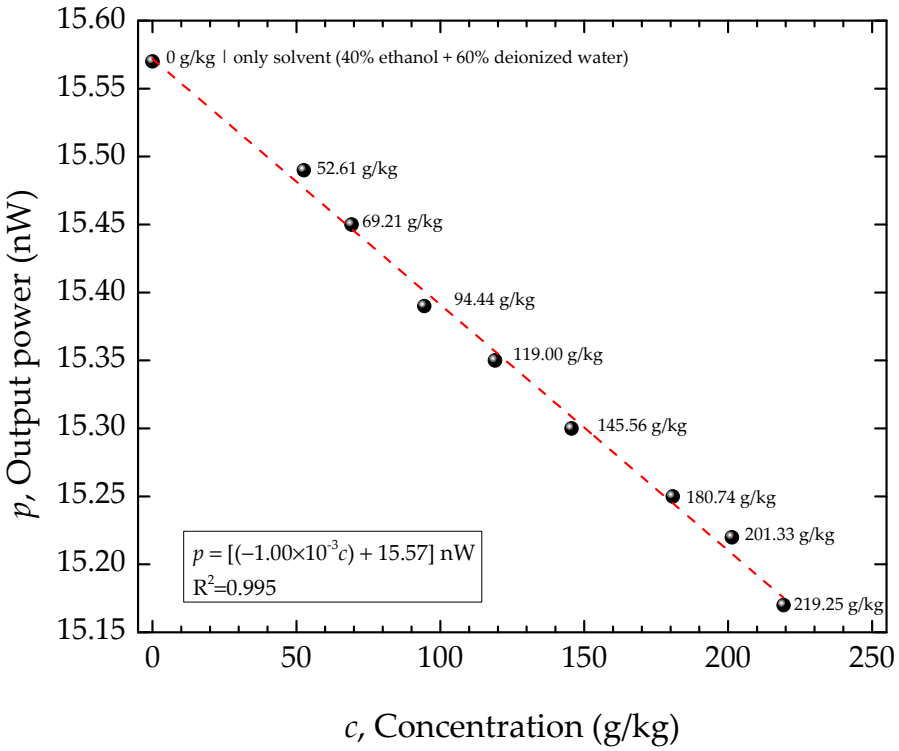

Figure 6. Output power levels as a function of paracetamol concentration in solution when the end of the reference port was immersed in the reference solution (40% ethanol and 60% deionized water) and sensing head was immersed in the paracetamol solutions.

From the results presented in Figure 6, a linear sensitivity of $\left[(-1.00 \pm 0.05) \times 10^{-3}\right]$ nW/(g/kg) to the variation of paracetamol concentration was obtained, with ranges of 52.61 to 219.25 g/kg.

3.3. Sensor Resolution

After the sensitivity evaluation, a step technique was applied for evaluating the resolution of the sensor: the sensing head was successively immersed in two paracetamol samples with consecutive values of concentration, and the sensor response (Figure 7), obtained using a power meter, was analyzed.

The minimum value of concentration (δ_c) that the sensor could discriminate was defined through the sensor response (Figure 7) using Equation (2) [9]:

$$\delta_c = 2\frac{\sigma_p \Delta c}{\Delta P} \tag{2}$$

where σ_p is the is the maximum standard deviation of the output power (5.0×10^{-3} nW) for both values of concentration (52.61 g/kg and 69.21 g/kg), Δc is the variation of concentration (16.6 g/kg), and ΔP is the mean displacement of output response between the two steps (3.0×10^{-2} nW).

Applying Equation (2), a resolution of 5.53 g/kg was obtained. It is important to mention that this value was also influenced by the spectral resolution of the equipment used for data acquisition.

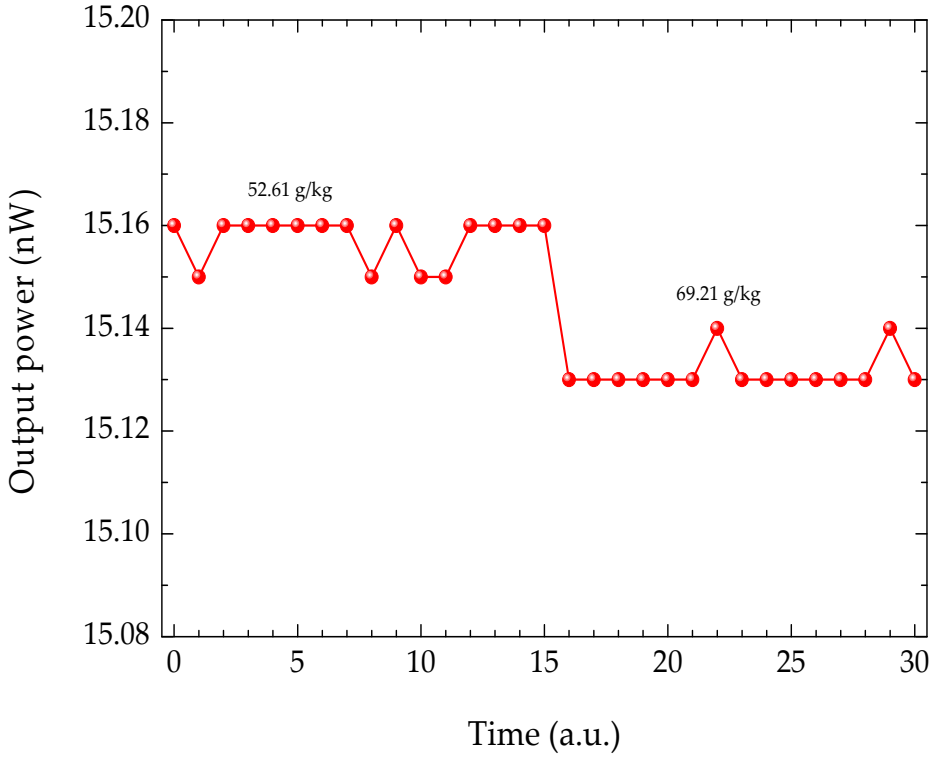

Figure 7. Step technique to estimate the sensing head resolution. The reference port was immersed in the reference solution (40% ethanol and 60% deionized water) and the sensing head was immersed, consecutively, in paracetamol samples with consecutive values of concentration, 52.61 g/kg and 69.21 g/kg, respectively.

4. Conclusions

In this work, an interrogation system based on an Erbium-Doped Fiber Ring Cavity was used to measure paracetamol liquid samples with different concentrations (range of concentrations between 52.61 to 219.25 g/kg).

The Cavity Ring proposed contemplates a 1×3 coupler; one of the ports corresponds to an FBG used as a reflector, and the two other ports are used as the sensing head and the reference, respectively.

During the measurements, the reference port remained vertically immersed in the reference medium, which was compounded by 40% ethanol and 60% deionized water (the solvent used in the paracetamol samples).

The sensing head allowed us to measure paracetamol concentrations with a sensitivity of $\left[(-1.00 \pm 0.05) \times 10^{-3}\right]$ nW/(g/kg) and a resolution of 5.53 g/kg.

The results obtained show the potential of the proposed configuration in monitoring the concentration of Active Pharmaceutical Ingredients (APIs), such as paracetamol.

Since the concentration is one of the most important parameters in pharmaceutical processes, the configuration proposed can be used to monitor this parameter in real-time and in a non-invasive way. In other words, the proposed technology can be considered a PAT tool with great potential in the pharmaceutical field.

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Conflicts of Interest: The authors declare no conflict of interest.

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