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RESEARCH ARTICLE

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# Development of a wearable surface enhanced Raman scattering sensor chip based on silver nanowires for rapid detection of urea, lactate and pH in sweat

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**Abstract.** A wearable sweat sensor chip based on surface-enhanced Raman spectroscopy (SERS) is here presented. The plasmonic core of the chip, obtained by deposition of silver nanowires on a polytetrafluoroethylene (PTFE) porous membrane, permits the direct and label-free detection of urea and lactate at physiologic concentrations in combination with the pH measurement in the range between 5 and 9. Once integrated with commercial biocompatible and adhesive tape layers, the as produced SERS-active chip provides a low-cost, flexible and wearable sensing device for rapid and reliable human sweat analysis. The chip was finally tested on real sweat samples to estimate lactate and urea during medium-intense exertions.

**Keywords:** Wearable sensor, SERS, Sweat, Urea, Lactate, pH, Silver nanowires.

## 1 Introduction

In the last decades, wearable sensors have received much attention thanks to their ability to provide useful information about metabolism and health of individuals [1]. Wearable devices originally developed for tracking physical exercise activity (*i.e.*, heart rate, burned calories, steps count) or to monitor biomedical parameters (*i.e.*, glucose concentration in blood) have stimulated major technological efforts to turn them into advanced biosensing platforms (lab-on-chip) for continuous monitoring of multiple health parameters and real-time sensing of physiological information with a potentially large impact in our daily lives [1, 2]. Sweat contains a broad variety of non-invasively accessible biomarkers that can provide key information directly related to body health in a continuous and on-demand way. Typical sweat components are electrolytes (sodium, potassium), metabolites (lactate, glucose, urea, uric acid, creatinine), minerals (calcium, magnesium, iron, zinc), amino acids (tyrosine, tryptophan), hormones (cortisol, testosterone) and proteins (C-reactive protein), with concentrations that ranges from mM to tenths of nM. Moreover, compared with other biofluids like blood, interstitial fluid, tear, saliva, and urine, sweat probing can be easily achieved by placing a sensor patch on accessible locations of the skin [2].

Surface-enhanced Raman scattering (SERS) is a spectroscopic technique that permits the label-free detection and vibrational characterization of analytes at sub-micromolar concentrations thanks to the plasmonic amplification of the Raman optical signals generated in proximity of noble metal nanoparticles surface (hot spots) [3, 4]. The possibility to easily integrate SERS-active layers onto flexible substrates, coupled with the recent availability of low-cost, miniaturized, handheld commercial Raman spectrometers, have paved the way for the development of optical technological platforms for the non-invasive healthcare monitoring by sweat inspection.

Recently, silk fibroin protein films were used in combination with silver nanoparticles, as a biocompatible layer for detecting lactic acid or drugs directly on the skin [5, 6]. Nanostructured polymeric films or membranes were decorated with noble metals and exploited as substrates for detection of lactic acid, uric acid, ascorbic acid from trace amounts of sweat [7–10]. More complex superhydrophobic/superhydrophilic layers were also combined with SERS active nanoparticles for detection of narcotics or physiological biomarkers, such as dopamine, creatinine or cortisol, in real sweat samples. [11, 12]. Moreover, SERS-active layers were functionalized with pH sensitive molecules [13], or combined with microfluidic circuits developed

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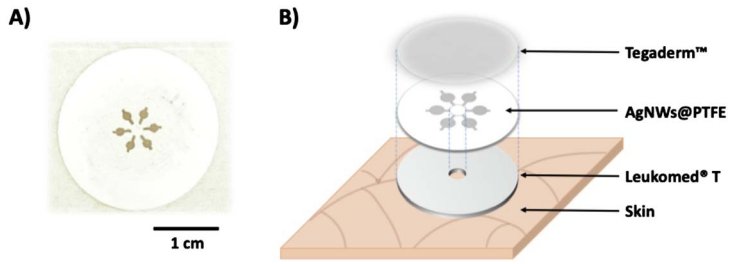


**Figure 1.** (A) Picture of a patterned AgNWs layer deposited on a hydrophobic PTFE filter membrane. Six 1.5 mm diameter circular spots are arranged with a radial bicycle spokes-like geometry. The AgNWs linear components have lengths of 2 mm and widths of 0.5 mm, respectively. (B) Schematic representation of a wearable SERS-active chip. The AgNWs@PTFE substrate is "sandwiched" between biocompatible and adhesive Tegaderm™ and Leukomed® T tapes. Both PTFE membrane and Leukomed® T tape are drilled in the centre in order to obtain an hole with a diameter of 2 mm that allows the direct flow of sweat from the skin to the hydrophilic AgNWs on top of PTFE. The Tegaderm™ tape instead acts as transparent and protective layer of the entire chip.

for collecting and guiding the sweat flow towards the sensor sensitive parts [14], in order to monitor the pH level of sweat or the content of its metabolites.

In this work we report the development of a SERS-active chip based on silver nanowires (AgNWs) deposited on a flexible polytetrafluoroethylene (PTFE) membrane. The SERS effect was successfully exploited for sensitive detection of urea and lactate from a model solution that mimics human sweat. By adding an additional functionalization step with a pH sensitive Raman probe, the AgNWs@PTFE substrate enabled the evaluation of sweat pH in the range of 5–9. Finally, the as-fabricated AgNWs@PTFE substrate was integrated with commercial, biocompatible and protective adhesive layers to obtain a fully flexible and wearable sensor chip for detection of analytes from sweat samples collected directly from the skin.

## 2 Materials and methods

AgNWs@PTFE chips were produced following the method recently reported by our group [4, 15]. In brief, 1 mL of commercial AgNWs dispersed in ethanol at concentration of 0.5 μg/μL (3D-nano Company, Poland), characterized by an average diameter of 100 nm and length ranging between 5 and 50 μm, were deposited by flow-through filtration (Amicon stirred cell 8003, Millipore) on a PTFE filter membrane (Sartorius, 25 mm diameter, 200 μm thick, pore size of 0.45 μm) with a final density of 0.1 $\mu g/mm^2$. The as-deposited AgNWs layer was patterned in 6 circular spots with 1.5 mm diameter and a radial geometry using a laser engraver (Neje, spatial resolution 0.45 mm, laser source tuned at 450 nm, max power 3W), in order to produce a hydrophilic and confined SERS-active region surrounded by a hydrophobic one (Fig. 1A). Laser pattern geometry includes the presence of an AgNWs rectangular channel radially arranged for each spot, with dimension of 2 mm in length and 0.5 mm in width, exploited for liquid flowing once the SERS chip is embedded with wearable tapes.

A human sweat model solution was prepared with the aim to test the SERS ability of the patterned AgNWs@PTFE membranes to detect urea and lactate at representative physiologic concentrations and to estimate the pH values. Simulated sweat (SS) was obtained by mixing (w/v) 0.1% urea, 0.1% lactate and 0.5% NaCl in ultrapure water (chemicals purchased by Merck), while the pH was fixed by using a phosphate buffer and tested by a bench pH-meter. The SERS activity of the substrate was studied varying the urea or lactate concentration from 0.01% (w/v) (1.67 mM) to 1.5% (250 mM), whereas the typical human physiologic values range between 5 and 200 mM. Each experiment was carried out by drop-casting 2 μL of analyte solution onto the AgNWs@PTFE spot, followed by waiting 1 min of incubation time and removal of the excess of liquid. All the experiments were conducted in triplicate and for three different pH values fixed at 4.8, 6.6 and 9.0. These values were selected to account for both the physiological mean pH value of sweat and any oscillations due to altered conditions.

A pH-sensitive probe molecule (4-mercaptobenzoic acid; 4-MBA) was employed to functionalize AgNWs and evaluate the pH level of sweat solutions [14]. Specifically, a spot of the as-fabricated AgNWs@PTFE was incubated for 12 h in a 4-MBA aqueous solution at $5 \times 10^{-5}$ M concentration, washed and dried in air.

In parallel, identical SERS chips were integrated in a biocompatible tape sandwich including Tegaderm™ (3M™) and Leukomed® T (Leukoplast®) as protective/adhesive and spacer layers, respectively, as shown in Figure 1B. More in detail, both AgNWS@PTFE membrane and Leukomed® T tape were drilled in the center in order to produce a hole with diameter of 2 mm that allows the direct flow of sweat from the skin to the hydrophilic AgNWs on top of PTFE membrane. On the contrary, the Tegaderm™ tape act as transparent and protective layer on top of the chip.

Experiments on real sweat sample were performed directly sticking the biocompatible SERS chip on volunteer's arm and collecting the secretion during moderate to intense physical exercise.

SERS spectra were acquired using a micro-Raman spectrometer (LabRam HR800 Evolution, Horiba) equipped with an excitation laser tuned at 785 nm, focused through a 50× LWD objective (Olympus, NA 0.5), and using a laser power at sample and integration time fixed at 400 μW and 5 s, respectively. For each sample, 30 spectra were acquired

on different position of the SERS substrate. The acquired spectra were pre-processed and elaborated using Labspec 6.0 (Horiba) and OriginPro (Origin Lab) software. Specifically, the spectra were normalized with respect to the peak centred at 1765 $cm^{-1}$ relative to the AgNWs@PTFE substrate, and the average spectrum was calculated and reported.

## 3 Results and discussion

The laser-patterned spot-deposition method recently described by our group [4, 15] guarantees a spatial control over the AgNWs area on PTFE, producing a confined SERS-active hydrophilic region surrounded by a hydrophobic one, as shown in Figure 1A. The immediate advantage is that few tens of μL of sweat secreted by the skin are enough to flow through the hole on the PTFE membrane and forced to be adsorbed on the AgNWs surface without the need of microfluidic channels.

Before the application of the wearable AgNWs@PTFE chip for sweat analysis, we firstly tested the ability of the patterned AgNWs layer on PTFE for the SERS detection of urea and lactate in simulated sweat (SS) at concentration values ranging between 0.01% and 1.5% (w/v) for three different pH values.

Figure 2 shows the SERS spectra of the SS for increasing concentration of urea, from 0.01% to 1.5% (w/v), and pH levels fixed at 4.8, 6.6 and 9.0. The spectra show a sharp dominant peak at 1002 $cm^{-1}$ relative to the C–N symmetric stretching vibration of urea, which increases in intensity at higher concentrations. C–N vibrations are also responsible of the less intense peak centred at 1410 $cm^{-1}$, while the peaks at 934 $cm^{-1}$, 1048 $cm^{-1}$, 1426–1451 $cm^{-1}$ are assigned to the $CH_3$ and CO modes of lactate [14, 16]. The area under the main vibrational peak of urea centred at 1002 $cm^{-1}$, in the spectral range from 950 to 1040 $cm^{-1}$ was employed for the calibration curve reported in Figure 2B. For all three pH values, a sigmoidal behaviour can be observed. The data were further reported in log–log graph, showed in the inset of Figure 2B, and fitted by a linear function in the range from 16 to 250 mM.

SERS spectra of SS at increasing concentrations of lactate are reported in Figure 3A. The intense urea peak observed in Figure 2A is still visible but less dominant due to the urea concentration set at 0.1% (w/v), making the intensity of the lactate Raman modes more appreciable in the spectral region between 813–875 $cm^{-1}$ and 1420–1450 $cm^{-1}$ [14]. A slight fluctuation of urea peak is also observed despite its concentration being constant. We hypothesize mutual interference between lactate and urea that alters its SERS response with increasing lactate concentration. However, these fluctuations are negligible compared to the signal variations observed with varying urea concentrations (Fig. 2A). The area of the vibrational band related to the C–C aliphatic stretching peaked at 853 $cm^{-1}$ was employed for calibration, as reported in Figure 3B. The data obtained exhibit a sigmoidal behaviour and when represented on a log–log scale as highlighted in the inset of Figure 3B, they adhere to a linear model in the range from 1.67 mM to 250 mM. These results confirm a concentration dependence of SERS response for these peaks, which is in accordance with the scientific literature [17–21].

As a proof of validation of the AgNWs@PTFE chip for detection and estimation of urea and lactate content in sweat, we also performed experiments using real sweat samples produced by a volunteer during physical exercise. Six different experiments were conducted and the SERS spectra are reported in Figure 4A. Specifically, these spectra were acquired under identical experimental conditions (laser wavelength, grating, detector) and normalized for laser power and integration time to ensure comparability with the spectra obtained from SS. The areas of the spectral regions assigned to lactate and urea vibrational bands, centred at 853 and 1002 $cm^{-1}$, respectively, were then calculated from the SERS spectra of real sweat and utilized for concentration estimation. Analysing the sweat from different rounds of physical activity, we detected lactate and urea concentrations ranging from 19 to 60 mM and from 50 to 80 mM, respectively, as shown in Figure 4B.

In order to improve the AgNWs@PTFE chip's sensing capabilities and expand its application to include sweat pH estimation, we functionalized the silver surface using a pH-sensitive molecule whose SERS spectral signature varies with pH. Some AgNWs spots on PTFE membrane were then incubated overnight in 4-MBA (see Materials and methods), allowing the formation of an effective pH-sensitive layer due to the formation of stable Ag–S bonds [14, 22]. We exploited the ability of 4-MBA to undergo a shift and an intensity variation of the Raman modes relative to the stretching of the carboxylate group (COOH) in the 1400–1425 $cm^{-1}$ spectral region as consequence of the pH changes [23]. In particular, 2 μL of PBS solution with pH values ranging between 1.1 and 12.0 were drop-casted on the spots functionalized with 4-MBA and were incubated for 1 min followed by removal of excess liquid. The variation of the pH values from 1.1 to 12.0 induces a red-shift and an intensity increase of the peak centred at 1400 $cm^{-1}$ (Fig. 5A). The changes become more evident at higher pH values, in which the carboxylate group vibration appears as a more intense and asymmetric band centred at 1425 $cm^{-1}$. On the contrary, pH variations do not affect the sharp peak assigned to the benzene ring breathing, centred at 1592 $cm^{-1}$ [23]. The pH calibration curve can be then obtained normalizing the area of the bands in the 1400–1425 $cm^{-1}$ interval to the area of the peak at 1592 $cm^{-1}$, as reported in Figure 5B. Such data, acquired in triplicate, can be described by a sigmoidal model function, with a linear trend in the pH interval between 5 and 9 and a correlation coefficient of 0.92. The AgNWs@PTFE functionalized with 4-MBA were moreover tested against three custom SS solutions at known pH values. The normalized areas of the 1400–1425 $cm^{-1}$ band are reported in Figure 5B as geometrical symbols (red diamond, blue square and purple circle) for pH equal to 4.8, 6.6, 9.0, respectively, in any case falling within the 95% prediction interval.

When SERS chips and their application as innovative platform for fast monitoring of health status by sweat

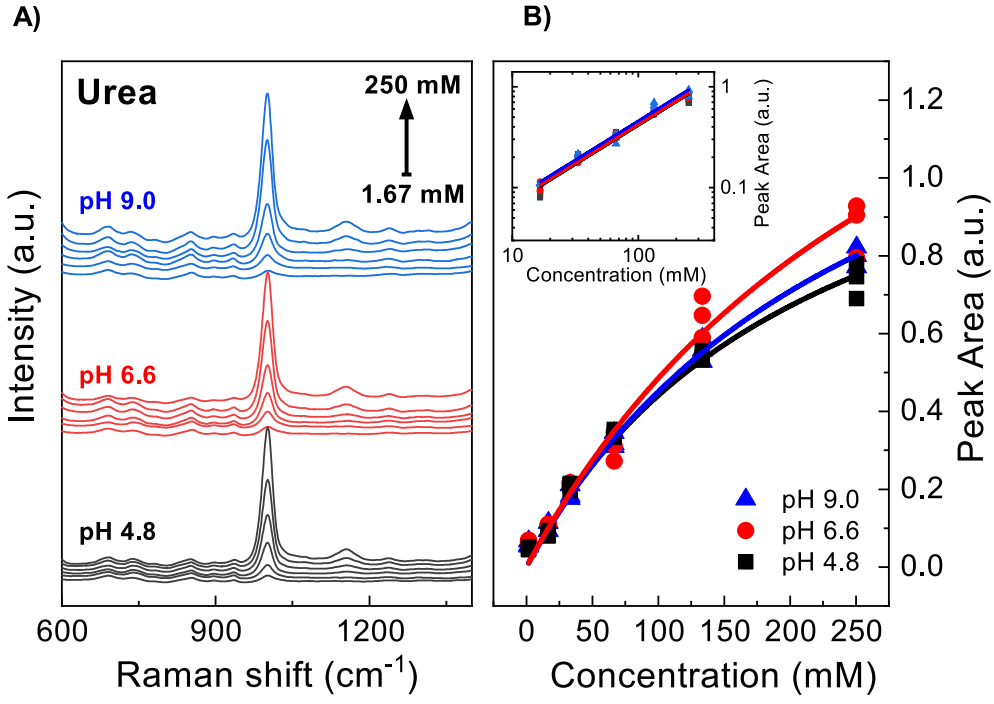


**Figure 2.** (A) SERS spectra of SS solutions at increasing concentrations of urea (0.01%, 0.1%, 0.2%, 0.4%, 0.8%, 1.5% (w/v)), acquired at three fixed pH values (black lines pH = 4.8, red lines pH = 6.6, blue lines pH = 9.0). The experiments were repeated three times on different AgNWs spots, the reported spectra represent the average of the three repetitions and were stacked for clarity. (B) Calibration curve obtained integrating the spectral raw data of the urea vibrational band comprised in the range 950–1040 $cm^{-1}$ and peaked at 1002 $cm^{-1}$ for each concentration value in three different experiments and for three pH values. Experimental data (scatter points) follow a sigmoidal model (coloured lines). The inset shows a log–log plot of the data, fitted by a linear function ($y = 4.10 + 0.77x$, $r^2 = 0.98$).

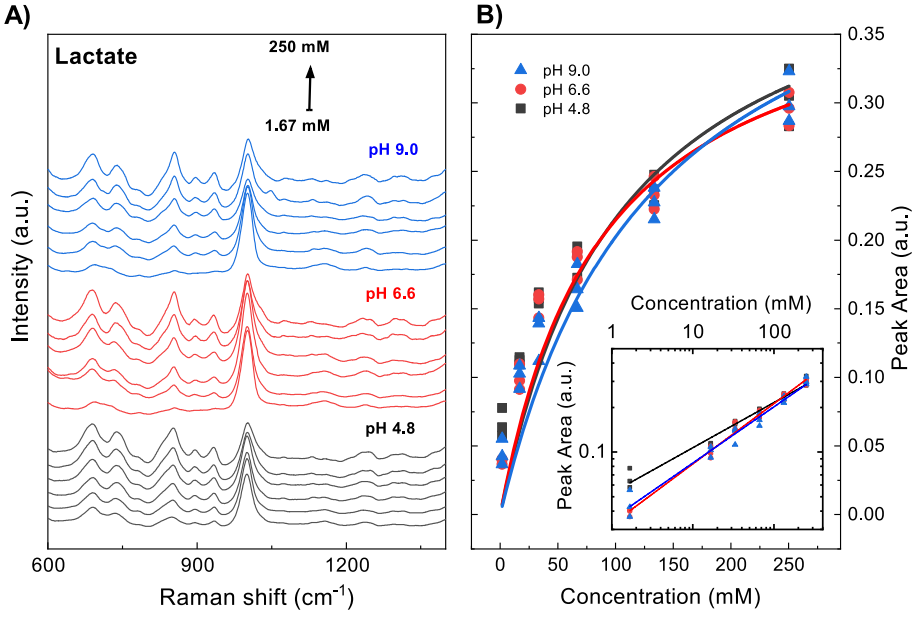


**Figure 3.** (A) SERS spectra of SS solution at increasing concentrations of lactate (0.01%, 0.1%, 0.2%, 0.4%, 0.8%, 1.5% (w/v)) acquired at three fixed pH values (black lines pH = 4.8, red lines pH = 6.6, blue lines pH = 9.0). The experiments were repeated three times on different AgNWs spots. The spectra reported represent the average of the three repetitions and were stacked for clarity. (B) Calibration curve obtained integrating the spectral raw data of the lactate vibrational band in the range 813–875 $cm^{-1}$ for each concentration value in three different experiments and for three pH values. Experimental data (scatter points) exhibit a sigmoidal behaviour (coloured lines). When reported in a log–log plot (inset) the data follow a linear model ($y = 4.72 + 0.30x$, $r^2 = 0.98$ at pH 4.8; $y = 4.51 + 0.39x$, $r^2 = 0.99$ at pH 6.6 and 9.0).

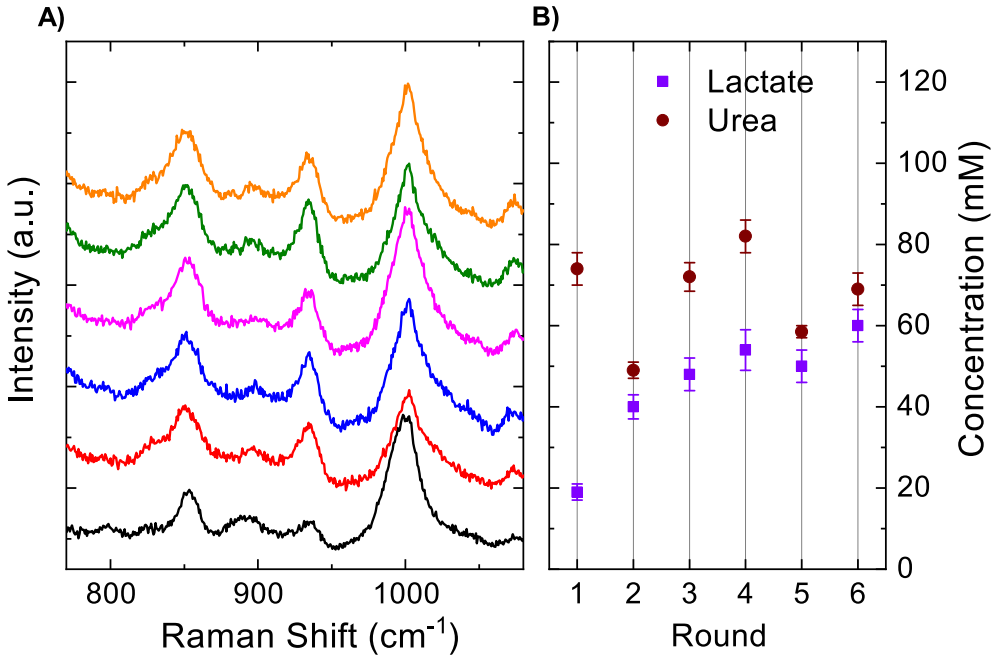


**Figure 4.** (A) SERS spectra of real sweat sample from a volunteer collected during six different rounds of physical exercise. Lactate and urea bands, centred at 853 and 1002 $cm^{-1}$, respectively, were used for estimating their concentration, as reported in panel (B) by using the calibration curves shown in Figures 2B and 3B.

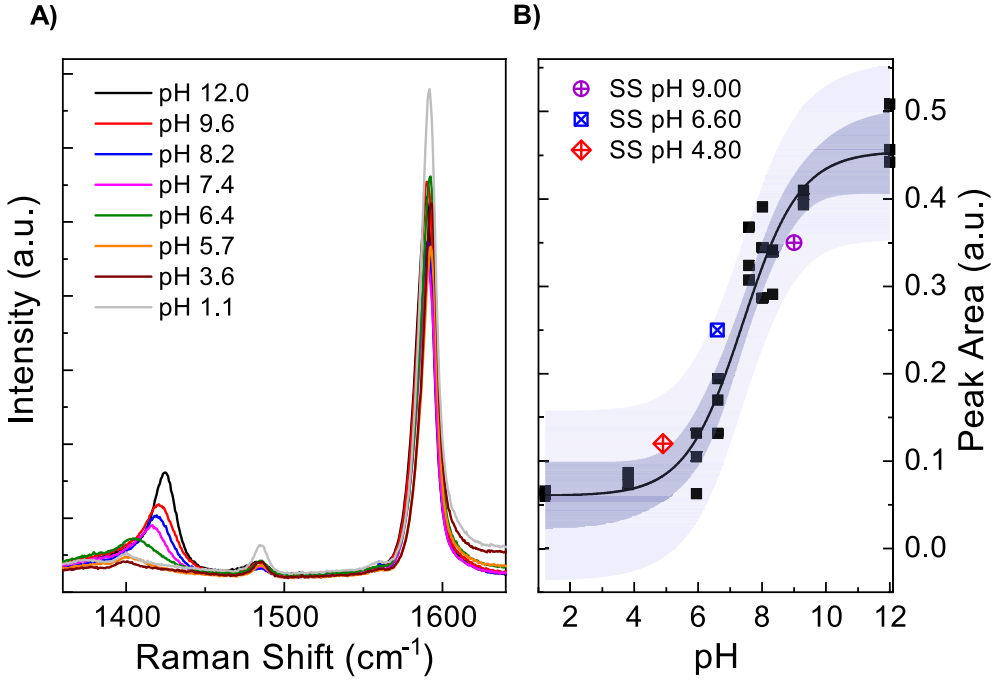


**Figure 5.** (A) SERS spectra of 4-MBA on AgNWs@PTFE after the incubation with 2 µL of PBS solution at different pH values. (B) Calibration curve obtained calculating the area under the bands in the 1400–1425 $cm^{-1}$ interval relative to vibration of the carboxylate group, normalized for the area of the peak centred at 1592 $cm^{-1}$ assigned to the benzene ring breathing mode. Calculated data (square symbols) are fitted with a sigmoidal function (black line) and the 95% confidence and prediction bands are reported in dark and light violet, respectively. Three SS solution with different pH values were used in order to test the chip and the obtained results are indicated with red, blue and purple geometrical symbols.

analysis are concerned, the manufacturing costs of the substrate must also be taken into account. At present, in our knowledge, there are no commercial SERS substrates on the market that meet the necessary flexibility and wearability requirements for such applications. Recent advancements in nanostructures production, affordability and signal reproducibility of substrates, led to a broader availability of commercial SERS platforms proposed by different companies [24–27]. These substrates are typically composed by a rigid glass support combined with a hydrophobic layer on which an area of few $mm^2$ is decorated with silver or gold nanostructures that act as sensitive region. Generally, the cost of these systems varies from 20 € to 80 € per substrate.

The wearable SERS chip here reported shows the advantage of being made up of only commercially available materials and do not require the application of technically complex and expensive fabrication procedures.

Moreover, both the instruments used for deposition by flow-through filtration (stirred cell) and laser patterning (laser engraver) of AgNWs require an initial total investment below 2 k€. We then tried to estimate the price of a wearable AgNWs@PTFE SERS chip calculated as the sum of the price of the AgNWs plus that of the PTFE filter membrane, of the chemicals needed for the deposition and of the biocompatible tapes used. In the calculation, we haven't considered labour cost, since it can be highly variable depending on the professional level of the operator and the country of production, nether we accounted for the cost of purchasing and managing the machinery. Considering an average cost of 30 €cents for the silver layer (1 mL of ten times diluted AgNWs solution), a unit prize of 3.75 € for each PTFE filter membrane and an average consumption of 2 mL of ethanol for dilution and preparation (ethanol 96%, price 51 €/L) a total cost of 4.15 € for each AgNWs@PTFE substrate can be estimated. Considering a 3 cm × 3 cm average area for both the Tegaderm™ (10 cm × 10 m non-sterile Roll, price 45 €) and Leukomed® T (8 cm × 10 cm patch, price 1.40 €/each) tapes, for the production of a wearable SERS chip a further cost of 40 €cents can be considered in addition to the aforementioned price. The final average cost per wearable SERS chip is thus below 5 €, at least 3 times less than SERS substrates commercially available. The competitive costs of the proposed AgNWs@PTFE platforms are furthermore supported by time-saving production processes, estimable in three different slots lasting 15 min each for silver deposition, laser patterning and embedding with biocompatible tapes, respectively.

## 4 Conclusions

In this work we describe a low-cost and time-saving method for producing a SERS sensor chip based on AgNWs deposited on PTFE, which allows the detection of urea and lactate at concentrations ranging from 1.67 to 250 mM. Such concentration range is compatible with typical physiological values of these metabolites in human sweat. The sensor chip was firstly calibrated using a simulated sweat solution, providing a linear response in the 4–250 mM and 1.67–250 mM ranges for urea and lactate, respectively. Moreover, upon functionalization with 4-MBA of AgNWs, we were able to measure the pH of simulated sweat by following the variation of the pH sensitive carboxylate vibrational mode normalized to that of the benzene ring of 4-MBA.

Furthermore, we reported on the integration of the SERS chip with commercial biocompatible tapes in order to obtain a wearable sensor patch for human sweat analysis. As proof of concept, the wearable chip was tested for the estimation of urea and lactate content from real sweat samples from a volunteer during several physical exercise rounds.

These results represent a significant advancement toward the development of a wearable and commercially-scalable sensor chip for sweat analysis by SERS spectroscopy, which could be easily implemented with portable Raman spectrometers for monitoring the health status of patients as well as the level of physical stress of athletes engaged in intense exercise sessions.

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#### Conflicts of Interest

All the authors declare no conflict of interest.

#### Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors on request.

#### Author contribution statement

CDA, PM: Conceptualization, Writing – original draft. CDA, MB, PM: Data curation, Investigation, Formal Analysis, Methodology, Visualization. CA: Investigation, Writing – review & editing. PP, FM, MdA, BH: Writing – review & editing. BW, PM: Supervision, Funding acquisition.

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