Detection of ibuprofen and aspirin on silver nets by surface enhanced Raman scattering (SERS) spectroscopy

N D Yarantseva¹, V N Belyatsky¹, E V Shleiko¹, E S Osotskaya¹, A A Burko², A L Dolgiy², K V Gire³ and H V Bandarenka²,³*

¹ Belarusian State Medical University, Minsk, 220116, Belarus
² Laboratory of Applied Plasmonics, Belarusian State University of Informatics and Radioelectronics, Minsk, 220013, Belarus
³ The Polytechnic School, Arizona State University, Mesa, AZ 85212, USA

h.bandarenka@bsuir.by, hbandare@asu.edu

Abstract. In this work, surface enhanced Raman scattering (SERS) spectra of aspirin and ibuprofen molecules adsorbed on the surface of silver nets sputtered on porous silicon were collected and analyzed. The bands in the SERS-spectra were correlated in accordance with the type of molecular vibration. Predominantly chemical adsorption of the indicated drugs on the SERS-active substrate through oxygen was observed. It was established that the Raman spectroscopy combined with the SERS-active silver nets makes it possible to detect the aspirin and ibuprofen at $10^{-6}$ M concentration.

1. Introduction
Since a very beginning of interest to Raman spectroscopy for the analysis of pharmaceutical polymorphs, use of this technique has dramatically increased in the pharmaceutical industry in particular for detection of painkillers [1, 2]. The Raman spectroscopy also has a potential to be used for a fast drug detection in physiological fluids. This method is based on the analysis of molecular vibrations and is sensitive to the chemical structure of molecule under study thus providing exceptionally high chemical specificity [3]. Ibuprofen (a derivative of phenylpropionic acid) and aspirin (a derivative of salicylic acid) are popular in pharmaceutics as non-steroidal drugs that have anti-inflammatory, analgesic and antipyretic effects. Due to the high availability of these drugs, people often take them without adhering to the recommended dosages and thinking about a significant number of side effects. For example, ibuprofen can increase the risk of heart, kidney, and liver failure. Taking aspirin increases the risk of gastrointestinal bleeding, can cause edema of skin tissues and even acute encephalopathy and fatty hepatosis in children and adolescents. Many patients are prescribed and use a constant daily dose of aspirin both in pure doses or as a constituent of some other pharmaceuticals. Chronic ingestion of aspirin can result in buildup of salicylic acid in the blood (salicylate poisoning) and is especially common among elders. The mild toxicity of salicylic acid (3–6 millimoles) has an effect on health whereas high toxicity can cause such symptoms as dysfunctions in renal and hepatic activity. In this regard, an extremely accurate determination of the submolar concentrations of these drugs in liquids for pharmaceutical industry and personal therapy is an urgent
task. SERS-spectroscopy has all the advantages of the Raman spectroscopy but provides working with lower concentrations of substances. SERS-spectroscopy is based on the detection of inelastically (Raman) scattered photons from molecules adsorbed on the surface of so-called SERS-active substrates consisting of metal nanoparticles, which are exposed to optical irradiation (visible or near infrared ranges). In this case, surface plasmons (quantums of vibrations of free electrons) are excited in the nanoparticles. The energy of plasmons is transferred to the adsorbed molecules, due to which the intensity of the analytical signal can be increased up to several tens of magnitude.

In this work, SERS-spectra of ibuprofen and aspirin were studied. The molecules of analytes were adsorbed on SERS-active substrates based on silver nets sputtered on porous silicon (PSi) from water solutions of $10^{-6}$ M aspirin and ibuprofen.

2. Experimental details

Fabrication process of SERS-active substrates included three steps. Firstly, samples of highly-doped $n$-type silicon wafer were electrochemically etched in a solution based on HF (45%) to grow a layer of PSi as described elsewhere [4]. In more detail the electrochemical processing was carried out with AUTOLAB PGSTAT302n potentiostat/galvanostat (Utrecht, The Netherlands) at 100 mA/cm$^2$ current density for 85 s. Then the PSi samples were treated in a mixture of 0.025 M CuSO$_4$·5H$_2$O water solution and HF (100:1 vol. ratio) for 5 s and in a diluted HNO$_3$ (10%) for 180 s. Finally the PSi samples were subjected to magnetron sputtering of silver films with 50, 100 and 150 nm thickness in NSC-3000 system (NANO-MASTER Inc., USA). Structural characterization of the samples was performed with scanning electron microscope (SEM) Hitachi-4800 (Tokyo, Japan).

SERS-spectra of organic analytes were studied with a 3D scanning laser confocal microscope equipped with a Raman photon detector, 473 nm laser and $\times 100$ (NA=0.95) objective (SOL Instruments, Belarus). The exposure time was 1 s. Micromolar solutions of rhodamine 6G, aspirin and ibuprofen in water were used as liquid analytes.

3. Results and discussions

The electrochemical etching of monocrystalline silicon wafer resulted in formation of the PSi layer with thickness 5 µm. The freshly prepared porous samples are characterized by bottle-necks of the pores causing uneven distribution of pore diameters (Fig. 1, a). Such a side effect causes irreproducibility of structural parameters of the silver film, which is deposited at the final fabrication step. An immersion of the PSi sample in the copper sulfate solution provided substitution of bottle-necked silicon skeleton with copper nanoparticles that then were removed in nitric acid solution. This led to an opening of an internal PSi structure with rather uniform pore diameters (Fig. 1, b). Silver coating of the PSi samples presented a kind of net constituted by spherical silver nanoparticles (Fig. 1, c-e). The silver nets inherited morphology of external surface of the underlying PSi. Mean diameter of the silver nanoparticles increases from 30 to 50 nm while the silver film is getting thicker. The nanoparticles’ boundaries are hardly distinguished, especially for the samples with silver films of 100 and 150 nm thickness, because they are interconnected in ligaments. It should be noted that such silver nanoparticles are known to intensively absorb blue light due to surface plasmon resonance (SPR) [5] but their coalescence in the elongated structures can potentially expand the SPR band to longer wavelengths of the visible range [6].

SERS-activity of the silver-coated PSi samples was analyzed using rhodamine 6G solved in water. This organic dye is typically applied in Raman and SERS-spectroscopies as a test analyte. Therefore its Raman spectrum is well-studied and is often used to compare SERS-activity of the substrates prepared at different conditions and regimes. SERS-spectra collected from the rhodamine 6G molecules adsorbed on the silver nets from micromolar solution are shown on Figure 2, a. All the samples were also scanned with the laser to create maps of distribution of a signal intensity at the 1366 cm$^{-1}$ band in the SERS-spectra of rhodamine 6G (Fig. 2, b). The most intensive SERS-spectrum
and the lowest signal deviation are observed for the thinnest silver film because it provides a lot of “hot spots” which are nanosized gaps between nearly connected silver nanoparticles. The samples with thicker films are characterized by graduate growth of the silver nanoparticles in diameter resulting in the gaps’ filling and formation of ligaments. The highest SERS-activity and the most uniform SERS-intensity distribution were the reasons to select the silver film with the 50 nm thickness for further detection of the drugs’ molecules.

**Figure 1.** SEM top images of (a) fresh PSi, (b) PSi after removal of the bottle-neck layer, PSi samples after sputtering silver film with thickness (a) 50, (b) 100 and (c) 150 nm.
Figure 2. SERS- (a) spectra and (b) maps (intensity of 1366 cm\(^{-1}\) band) of rhodamine 6G molecules adsorbed on the silvered PSi.

Figure 3 shows the SERS spectra and structure of aspirin and ibuprofen molecules adsorbed on the surface of silver nets on PSi from the solutions with the drugs’ concentration of \(10^{-6}\) M. The peaks observed in the SERS spectra are the characteristic Raman bands of the analytes. We observed strong C-O-C (808 cm\(^{-1}\)) vibrations and vibrations in the hydroxyl plane associated with the carboxyl group (1626 cm\(^{-1}\)) in the SERS-spectrum of aspirin. This indicates that analyte molecules were chemisorbed on the silver surface through oxygen. It was revealed that strong vibrations correspond to carboxyl group (1614 cm\(^{-1}\)) in the structure of ibuprofen. This also signify that molecules of ibuprofen are chemosorbed on the silver surface through oxygen.

![Figure 3. SERS-spectra of (a) aspirin and (b) ibuprofen molecules adsorbed on the silvered PSi.](image)

The presence of intense bands at 156 and 218 cm\(^{-1}\) in the SERS spectra (the range is not shown in the images) of both substances which are associated with stretching vibrations (valence vibration) of the silver-oxygen bond is confirmed the chemisorption of aspirin and ibuprofen on the silver net.

4. Conclusion
Solid SERS-active substrates constituted by the silver nets on PSi were fabricated and characterized. It was found that the silver net with the 50 nm thickness provides the highest SERS-activity and the most uniform signal distribution. It was established that the indicated SERS-active silver net makes it possible to detect the aspirin and ibuprofen molecules at \(10^{-6}\) M concentration, which is usually achieved in a case of using colloidal SERS-active substrates, characterized by the instability of measurement results and inconvenience of use.

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