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Determination of pesticides by capillary chromatography and SERS detection using a novel Silver-Quantum dots "sponge" nanocomposite

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ABSTRACT

In this work the at-line capillary-liquid chromatography-(microdispenser)-surface-enhanced Raman spectroscopy coupling was investigated and applied to the determination of pesticides. The use of a microdispenser combined with the use of a precise and reproducible surface enhanced Raman spectroscopy (SERS) substrate yielded a chromatographic detection system with excellent analytical properties. The microdispenser was coupled to a moving CaF_2 hot (80 °C) plate using a flow-through microdispenser interface to collect the microdrops. Ag-QD nanocomposites, which are highly reproducible thanks to their sponge-shaped structure, were used as substrate with which to measure the SERS spectra in each spot of the plate. The limits of detection ranged from 0.2 to 0.5 ng of pesticide injected (chlortoluron, atrazine, diuron and terbuthylazine) and the precision ranged between 10.2 and 12.5%.

1. Introduction

The development of different approaches to couple modern separation systems with infrared and Raman spectroscopy is an ongoing field of research because, for analyte identification and fundamental studies, modern spectroscopic techniques that provide a full spectrum are required. Among these, infrared and Raman spectroscopy are of special interest due to the molecular specific fingerprint that they provide [1,2]. However, although the hyphenation of high performance liquid chromatography (HPLC) with mass spectrometry (MS), nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR) is well known and, in many cases, commercial equipment and interfaces are available, the coupling of HPLC and Raman spectroscopy is still at an exploratory stage [3]. Raman spectroscopy is an interesting spectroscopic technique with which to perform fundamental studies, for example molecular interactions whilst additionally, contrary to IR, it does not suffer from the strong absorption of water. Despite such advantages, Raman scattering suffers from the disadvantage of relatively poor sensitivity [4,5]. To overcome the low sensitivity, a more sensitive variant, surface enhanced Raman spectroscopy (SERS), may be considered for certain applications. SERS has been proven to be a powerful method for the detection of very low concentrations [6–10]. Compared to normal Raman spectroscopy, the signal intensity is significantly increased due to the interaction with surface plasmons formed on colloidal metal structures by the incident laser light and the analyte molecules under investigation [11–13].

Several efforts have been undertaken to couple HPLC and SERS. SERS is most easily coupled to LC in the at-line mode [14], although on-line approaches have also been described in the literature [15,16]. This may be related to the fact that LC eluents frequently contain organic modifiers, buffer salts and other additives which, not only may cause considerable Raman spectral interferences but, more importantly, may have detrimental effects on the SERS activity of the sol. The above mentioned constraints can be circumvented by immobilizing the LC chromatogram on a thin-layer chromatographic (TLC) plate prior to SERS measurement of the analytes. In this way, Seifar et al. deposited the analytes on silica TLC plates [14] and Schneider et al. collected the active compound of illicit drugs in the wells of a microtiter plate containing a gelatin stabilized silver halide [17]. However, the main disadvantage of those methodologies is the inhomogeneous distribution of the deposited drops, which prevent their use for quantitative purposes. Other proposed alternatives to couple Raman detection to liquid chromatography are the use of a heated gas nebulizer [18], concentric flow nebulizer [19–21], ultrasonic nebulizer [22,23], electrospray nebulization [24] or thermospray interface [25–27]. None of these strategies provide sufficient robustness. Alternatively, the use of a

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flow through microdispenser which is capable of producing 50 pL sized microdroplets is the most promising and suitable strategy to achieve small deposits in a controlled way [28,29]. The usefulness of these microdispensers has already been demonstrated in different hyphenated systems such as LC-MALDI-MS [30–32] or LC-FTIR systems [33].

The aim of this paper is to study the potential of a microdispenser as an at-line interface between capillary-LC and Raman spectroscopic detection, together with the SERS technique, using a novel nanocomposite of Silver-Quantum dots as an active substrate. The combination of the micro separation system with the microdispenser allows a simple approach for SERS detection whilst on the other hand, the use of the nanocomposite provides a sensitive and robust detection system. In combination, this system facilitates the analysis of analytes in the sub-nanogram range.

2. Experimental

2.1. Reagents and materials

All chemical reagents were of analytical grade and used as purchased with no additional purification. Cadmium oxide (99.99%), trioctylphosphine oxide (TOPO, 99%), trioctylphosphine (TOP, 90%), selenium (powder, 100 mesh, 99.99%), diethylzinc solution ($ZnEt_2$, ~1 M in hexane), bis(trimethylsilyl) sulphide ($(TMS)_2S$), anhydrous methanol and anhydrous chloroform were purchased from Sigma Aldrich (Madrid, Spain). Hexylphosphonic acid (HPA) was obtained from Alfa Aesar (Karlsruhe, Germany). Methanol (HPLC grade) was purchased from Sigma (Schnelldorf, Germany). Chlortoluron (99.8%), atrazine (97.4%), diuron (99.5%) and terbuthylazine (98.6%), all of them Pestanal grade standards, were purchased from Riedel-de-Haen (Seelze, Germany).

Stock solutions of the pesticide mixture (1000 $\mu g\,mL^{-1}$) were prepared in methanol and stored at 4 °C. Diluted standards were prepared from this solution by appropriate dilution in the mobile phase.

2.2. Preparation of the SERS-active substrate

A very high-SERS-active Ag-QD nanostructure is used as a novel and very promising SERS substrate. Both the optimization in our Ag-QD preparations and the characterization of these nanocomposites were performed in detail in an earlier work [34]. Briefly, core–shell quantum dots (ZnS-capped CdSe) were synthesized using CdO as precursor [35–37]. Then, 0.2 mg of CdSe/ZnS QDs were dispersed in 5 mL of a solution of hydroxylamine 8.5×10^{-3} M with 0.04 mL of NaOH 2 M. The hydroxylamine-QDs dispersion was rapidly added to 45 mL of an aqueous solution of silver nitrate (1.1×10^{-3} M) under vigorous stirring. Finally, the mixture was allowed to stir for additional 10 min. Fig. 1 shows characteristic SEM images of the produced SERS active sponge consisting of colloidal silver prepared in the presence of CdSe/ZnS nanoparticles.

2.3. Instrumentation

The capillary LC chromatographic system consisted of an Ultimate 3000 Dionex with a 1 μL injection loop and a C18 Acclaim PepMap (300 μm ID × 15 cm, 3 μm, 100 Å) separation column from (Dionex Corporation, GmbH, Germany). The column was kept at 40 °C and the experiments were performed with a 3 $\mu L\,min^{-1}$ eluent flow rate. For the separation, methanol was used as solvent A and deionized water was used as solvent B and the following multi-steps gradient were used: 0 min 50% A, 20 min 70% A, 22 min 100% A, 33 min 100% A, 36 min 50% A, 40 min 50% A. All the eluent was transferred to the microdispenser without flow splitting. A variable wavelength UV–vis detector (Ultimate UV Detector, LC Packings, Dionex) set at 224 and 248 nm was placed before the microdispenser interface. An in-house developed program based on LabVIEW 8.5 software (National Instruments, Austin, USA) was used to control the UV spectrometer and register the chromatograms. The UV detection window was made in the untreated fused silica capillary (i.d. 50 μm, o.d. 363 μm) by burning away a small piece of surrounding polyamide coating on the capillary.

The flow-through microdispenser interface is a micro-liquid handling device formed from two silicon structures by conventional micromachining. The piezoceramic element of the dispenser was driven by a DC power supply (HGL 5630 DLBN) together with a computer controlled arbitrary waveform generator (Agilent 33120A, Agilent Technologies, Palo Alto, CA) which provided an electronic pulse with defined amplitude (15 V), rise (5 μs), width (490 μs), and decay time (680 μs). To enable lateral location of the deposits on the CaF_2 (80 mm × 19 mm × 2 mm) target, a computer controlled *x*,*y*-stage (Newport THK, Compact Linear Axis) with step sizes of 5 μm and maximum distance of 90 mm × 40 mm was implemented in the dispensing unit. A heatable sample holder A599 Bruker (Bruker GmbH, Ettlingen, Germany) with a maximum temperature of 180 °C was used to control the temperature of the CaF_2 window. The microdispenser was connected to the capillary LC column via a fused silica capillary (i.d. 50 μm, o.d. 364 μm, and 40 cm long). All the computer controlled components of the microdispensing unit were operated with the help of an in-house-written MS Visual Basic 6.0 (Microsoft) based software program (Sagittarius, Version 3.0.25) working under Windows NT.

Raman measurements of deposits of analytes were acquired with a confocal Raman microscope (LabRaman HR, Jobin Yvon Ltd., Bensheim, Germany) using a 633 nm laser line (17 mW) and a charge coupled device (CCD) detector with 1024 × 256 pixels. A grating with 600 grooves/mm, a confocal aperture of 500 μm and an entrance slit of 100 μm were selected for the experiments. A 100× microscope objective was used to focus the laser beam on the CaF_2 plate, as well as to collect the scattered photons.

2.4. Separation and detection of pesticides

2.4.1. Continuous system

In order to obtain the maximum information regarding the chromatographic separations, the working conditions of the microdispenser were optimized to collect the maximum number of drops possible for subsequent Raman analysis. The working conditions of the stage – dispensing unit were as follows: initially it was stationary for 1140 s, then moved with a fast translation of 1 mm (at 1000 μm per second) and stopped for 10 s whilst the dispenser was working, with a dispensing frequency of 100 droplets per second. This program was repeated until the end of the chromatographic separation. In this way each analyte was present at three or four points along the plate, producing a representation of a 3D chromatogram.

2.4.2. Optimized system for increased sensitivity

To obtain the maximum sensitivity, the stage microdispenser was programmed to collect the maximum amount of each analyte at the same point on the CaF_2 plate. The optimal working conditions for the stage-microdispenser unit were fixed according to the elution time of each analyte and the separation between them, and were as follows: (see Fig. 2B). First the unit was stationary for 1140 s before initiating the working cycle. This cycle comprised two steps, a fast translation of 1 mm (at 1000 μm per second) and a stop of 40 s whilst the dispenser was working with a dispensing frequency of 100 droplets per second, and was repeated 6 times. Then, the stage-microdispenser unit was stationary for a further 260 s before repeating the above program twice. During the whole deposition

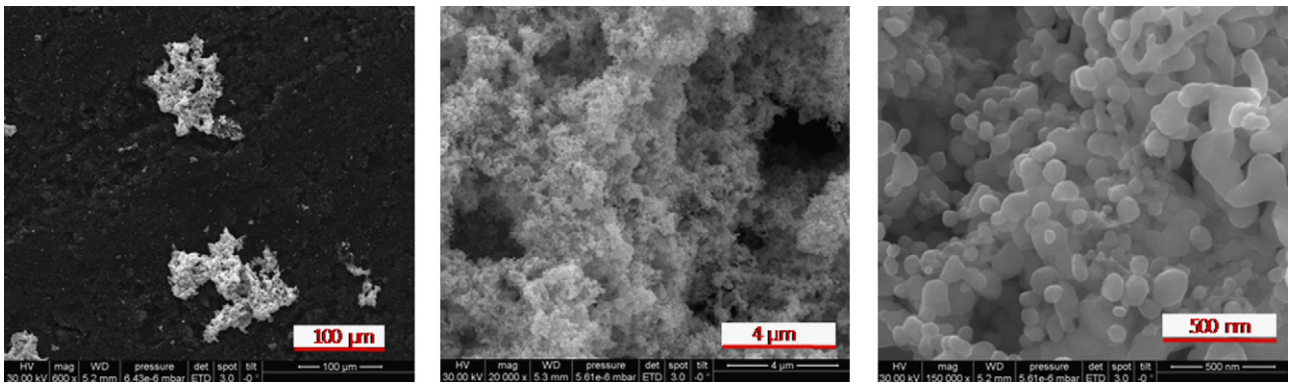

Fig. 1. SEM images of the produced Ag-QD colloid.

process the temperature of the sample holder was maintained at 80 °C.

2.4.3. Measurement of Raman and SERS spectra

In both cases the Raman and SERS measurements of the deposited chromatograms were carried out in the same way. First, the Raman spectra of each analyte were recorded from each deposited spot. Positioning of the Raman microscope at each analyte spot on the trace was achieved by means of a manually controlled *x*,*y*-stage. Subsequently, aliquots of the colloidal Ag-QD solution (1 µL) were cast using a Hamilton syringe and air-dried on each analyte spot for SERS spectra collection. In all cases spectra were recorded with a data acquisition time of 20 s and were baseline corrected.

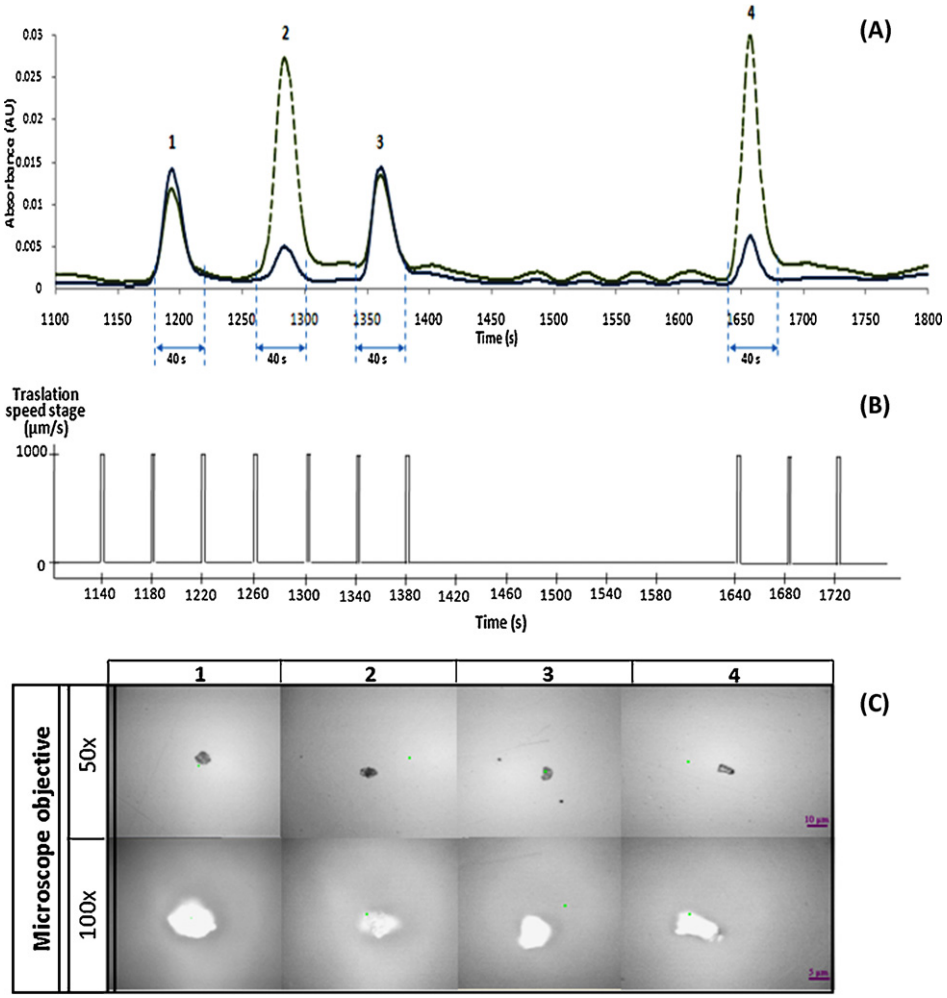

Fig. 2. (A) The µLC-UV chromatogram of the four pesticides, recorded by absorbance detection at 224 and 248 nm, for a mixture standard solution of 10 µg mL^{-1} (10 ng injected on column); peak 1: chlortoluron, peak 2: atrazine, peak 3: diuron, peak 4: terbuthylazine (B) The programmed performance of the microdispenser-stage; (C) microscopic images of the solid deposits of the different analytes from a 10 µg mL^{-1} pesticide standard injected.

3. Results and discussion

3.1. Microdispenser as at-line interface

The coupling of the microdispenser with the chromatographic system allows the continuous deposition of fractions (microdrops), from the flow coming from the chromatographic column, onto a CaF_2 target plate. As the plate is heated to 80 °C, after deposition, the solvent evaporates, resulting in the formation of crystalline deposits.

Multicomponent standard solutions of the four pesticides were separated by *capillary* LC under the conditions described in Section 2. The absorbance at 224 and 248 nm was recorded using a UV spectrometer placed immediately before the microdispenser interface. Fig. 2A shows a typical chromatogram of the four pesticides recorded by absorbance detection at 224 and 248 nm when a standard solution of 10 μg mL^{-1} (10 ng injected on column) for each pesticide was injected. Under the optimized conditions of the stage-dispensing unit, to obtain the maximum sensitivity (described in Section 2.4), the chromatographic trace consisted of solid deposits of the sequentially eluted analytes from a 10 μg mL^{-1} pesticide mixture standard. The programmed performance of the microdispenser-stage is depicted in Fig. 2B. The size and shape of the spots obtained for the different analytes are shown in Fig. 2C. These images were recorded with the Raman microscope using the 50× microscope objective (top) and the 100× microscope objective (bottom). As can be seen, the spot diameters were of ca. 10 μm, although the spot size varies depending on the amount of analyte deposited on the plate.

Based on the results from previous studies carried out with the same microdispenser [38], the working conditions were re-evaluated in order to obtain smaller and more compact analyte spots. Slight changes in the droplet appearance, due to differences in surface tension of the solution, can be controlled by modification of the applied electrical pulse driving the piezoceramic element. Improved results were obtained with an amplitude of the signal of 2.5 V and a DC offset of 1.25 V. In general, a higher speed will result in a better resolution on the plate, but obviously this will be at the expense of sensitivity. The stage-microdispenser was operated under the optimal working conditions described in Section 2. In these conditions the dispenser's precision was very acceptable. It was found that more homogeneous deposits could be obtained for lower concentrations of the analyte.

3.2. SERS detection

To optimize the procedure of the SERS analysis of the deposited compounds, preliminary experiments were performed by manual deposition of the analytes and the SERS-active solution on the plates, using a Hamilton syringe. First, three different types of plates (CaF_2, ZnSe and glass) were compared. The CaF_2 plate was found to be a better substrate than glass because of the more compact spots obtained, and consequently, higher sensitivity and better spatial resolution were achieved. In a second study, the deposition order of the analytes and the SERS-active solution was studied. In the first proof, the Ag-QD nanoparticles (NPs) were first deposited on the plate and after the droplet with the analyte was placed above. This procedure did not produce good results because the previously deposited Ag-QD NPs are just immobilized by adsorption and when the methanolic solution of the analyte is added on top, the NPs are removed. In a second approach, the analytes were deposited on the plate first and then the colloidal Ag-QD solution was added on each spot. This approach leads to very good and reproducible results. This procedure has already been reported in previous works [14,39,40].

The Raman and SERS spectra shown in Fig. 3 were recorded using an injected a concentration of 10 μg mL^{-1} for each pesticide. With an injection volume of 1 μL, and without flow splitting, the total amount of each pesticide injected in the μLC column is 10 ng. Therefore, under the above mentioned dispenser's working conditions and considering that the volume of each drop is 50 pL [28], the corresponding amount of analyte deposited on the plate is ca. 1 ng.

The deposition process and the interaction of the analytes with the plate do not disturb the spectral shapes. The Raman spectra were recorded from each deposited spot and then SERS spectra were recorded after the addition of Ag-QD solution to each spot.

As can be seen in Fig. 3, the Raman intensity of all analytes (measured at the same point) increased significantly after the deposition of the Ag-QD colloid by a factor between 7 and 10 (depending on the analyte). The enhancement factor was calculated using the following equation:

$$\mathrm{EP} = \left(\frac{N_{\mathrm{Ranman}}}{N_{\mathrm{SERS}}}\right) \cdot \left(\frac{I_{\mathrm{SERS}}}{I_{\mathrm{Ranman}}}\right).$$

where I_{SERS} and I_{Raman} are the SERS intensity and the normal Raman scattering intensity of one of the Raman line of each pesticide, respectively. N_{SERS} and N_{Raman} are the number of molecules in the probing volume after and before adding the Ag-QD colloid, respectively. N_{SERS} and N_{Raman} were assumed to be equal as we used the same configuration and both Raman and SERS signals were measured at the same point.

It must be noted that spot diameters increased to ca. 20–25 μm after the addition of Ag-QD solution, but this increase in spot size did not affect the spatial resolution. Good quality SERS spectra were recorded for all analytes. The spectra of the two triazines and those of the two phenylureas are, of course, rather similar, but many significant spectral differences in the 1800–200 cm^{-1} region allowed their unequivocal identification and mutual discrimination.

It is important to remark that the SERS intensities obtained with the Ag-QD colloid were significantly greater than those obtained from Ag colloids without QDs as we previously reported [34]. The higher SERS activity of the Ag-QD colloid was attributed to several reasons: (i) the silver aggregates obtained in the presence of QDs present a higher size, and this different degree of aggregation of the silver colloid can be responsible for the SERS enhancement; (ii) some QDs act as a spacer between silver nanoparticles and, by means of this, to generate 'hot spots' which contribute to an increase in the overall observed enhancement factors; and (iii) QDs also act as co-reductor of the reaction together with the hydroxylamine, leading to a different silver structure with a particular spongy-morphology which is more active in SERS.

3.3. Analytical features of the capillary LC-(microdispenser)-SERS method

The new capillary LC-(microdispenser)-SERS methodology was also evaluated in terms of sensitivity, limits of detection (LOD), quantification (LOQ) and precision and the results obtained are summarized in Table 1. The analytical signal used was the Raman intensity at 780 cm^{-1} for chlortoluron, 960 cm^{-1} for atrazine, 1230 cm^{-1} for diuron and 960 cm^{-1} for terbuthylazine. Calibration graphs were constructed by plotting the Raman intensity of the selected peak for each analyte versus the pesticide concentration injected in the column (Fig. 4). It is, of course, interesting to estimate the detection limits obtained with this technique. To determine the limits of identification, various dilutions of the four pesticide mixture were analyzed. The deposits from a diluted sample of 0.2 μg mL^{-1} still yielded identifiable spectra for all pesticides. From these spectra the identification limits were estimated to be 0.1–0.2 μg mL^{-1} depending on the pesticide. At these concentrations, the deposited spots of the analytes could no longer be localized visually. Interestingly, they could be determined quite

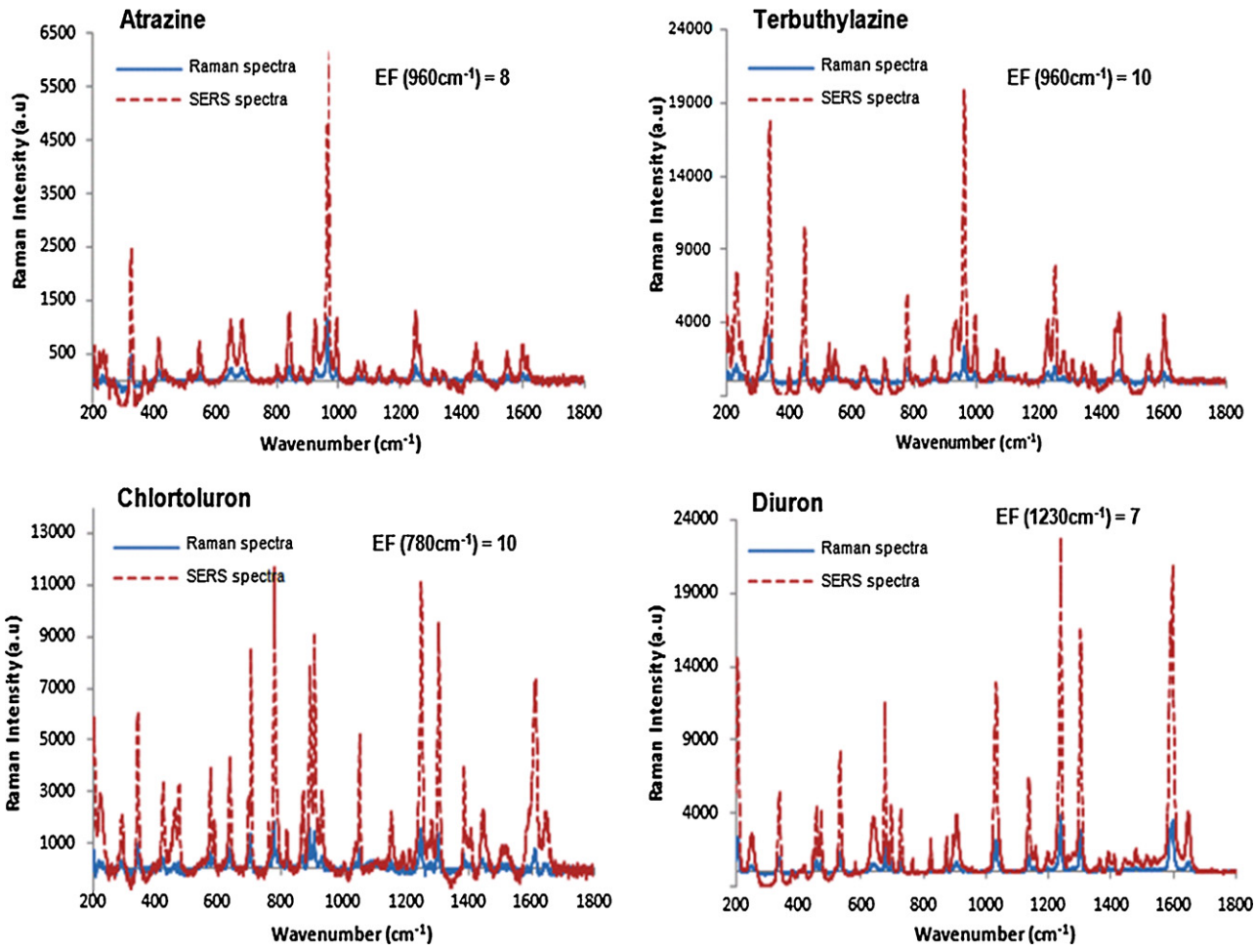

Fig. 3. Raman and SERS spectra of the four pesticides for 10 μg mL^{-1} injected on μLC column. All spectra were collected using acquisition times of 20 s.

accurately on the basis of retention times and the speed of the CaF_2 plate during deposition. It should be emphasized that the deposited amounts were dispersed on the plate in spots of ~10 μm^2 as can be seen in Fig. 2C. Only a minor fraction of each spot was irradiated by the laser beam, which had a cross section of ~1 μm^2 when the 100× microscope objective was used. Therefore, the spectra recorded represent no more than a few picograms of pesticide.

In order to study the repeatability of the proposed method, five independent analysis of 10 μg mL^{-1} was carried out and the RSD obtained was between 10.2 and 12.5% depending on the studied analyte.

Finally, the 3D SERS chromatogram obtained under the recommended working conditions is depicted in Fig. 5. As can be seen, each analyte was found in three or four points along the plate allowing the representation of a 3D chromatogram.

In Table 1 the analytical features of the proposed method and those obtained with the same microfluidic system and performing the on-line detection with a UV spectrometer are summarized. As

Table 1
Comparison of analytical features of the μLC-UV and μLC-(microdispenser)-SERS methods for the determination of chlorinated pesticides.

	μLC-UV				μLC-(microdispenser)-SERS			
	Chlortoluron	Atrazine	Diuron	Terbuthylazine	Chlortoluron	Atrazine	Diuron	Terbuthylazine
Retention time (min)	19.8	21.3	22.7	27.7	19.8	21.3	22.7	27.7
Analytical signal	Absorbance (248 nm)	Absorbance (224 nm)	Absorbance (248 nm)	Absorbance (224 nm)	Raman Int. (780 cm^{-1})	Raman Int. (960 cm^{-1})	Raman Int. (1230 cm^{-1})	Raman Int. (690 cm^{-1})
Regression equation	$y = 0.0271x - 0.0382$	$y = 0.0485x + 0.0141$	$y = 0.0294x + 0.0257$	$y = 0.0515x - 0.0559$	$y = 1137.9x - 0.6$	$y = 646.96x + 0.3$	$y = 1845.5x - 0.2$	$y = 1655.8x - 0.8$
Linearity (R^2)	0.9922	0.9946	0.9928	0.9954	0.9775	0.9754	0.994	0.9876
LOD (μg mL^{-1})[a]	1.5	1.1	1.3	1.0	0.2	0.2	0.1	0.1
LOQ (μg mL^{-1})[b]	5.0	3.7	4.3	3.3	0.5	0.5	0.5	0.5
RSD (%)[c]	4.4	7.2	5.0	4.0	11.9	12.5	10.2	11.3

[a] LOD established as 3 times the standard deviation of five replicates of 10 μg mL^{-1} standard pesticide mixture divided by the slope of the calibration line (for the μLC-UV method) and calculated experimentally doing dilutions of the pesticide mixture standard until still yielded identifiable spectra for each pesticide (for the μLC-microdispenser-SERS method).

[b] LOQ established as 10 times the standard deviation of five replicates of 10 μg mL^{-1} standard pesticide mixture divided by the slope of the calibration line (for the μLC-UV method) and the lower concentration of the calibration line (for the μLC-microdispenser-SERS method).

[c] Relative standard deviation value of five independent analysis of 10 μg mL^{-1} standard pesticide mixture.

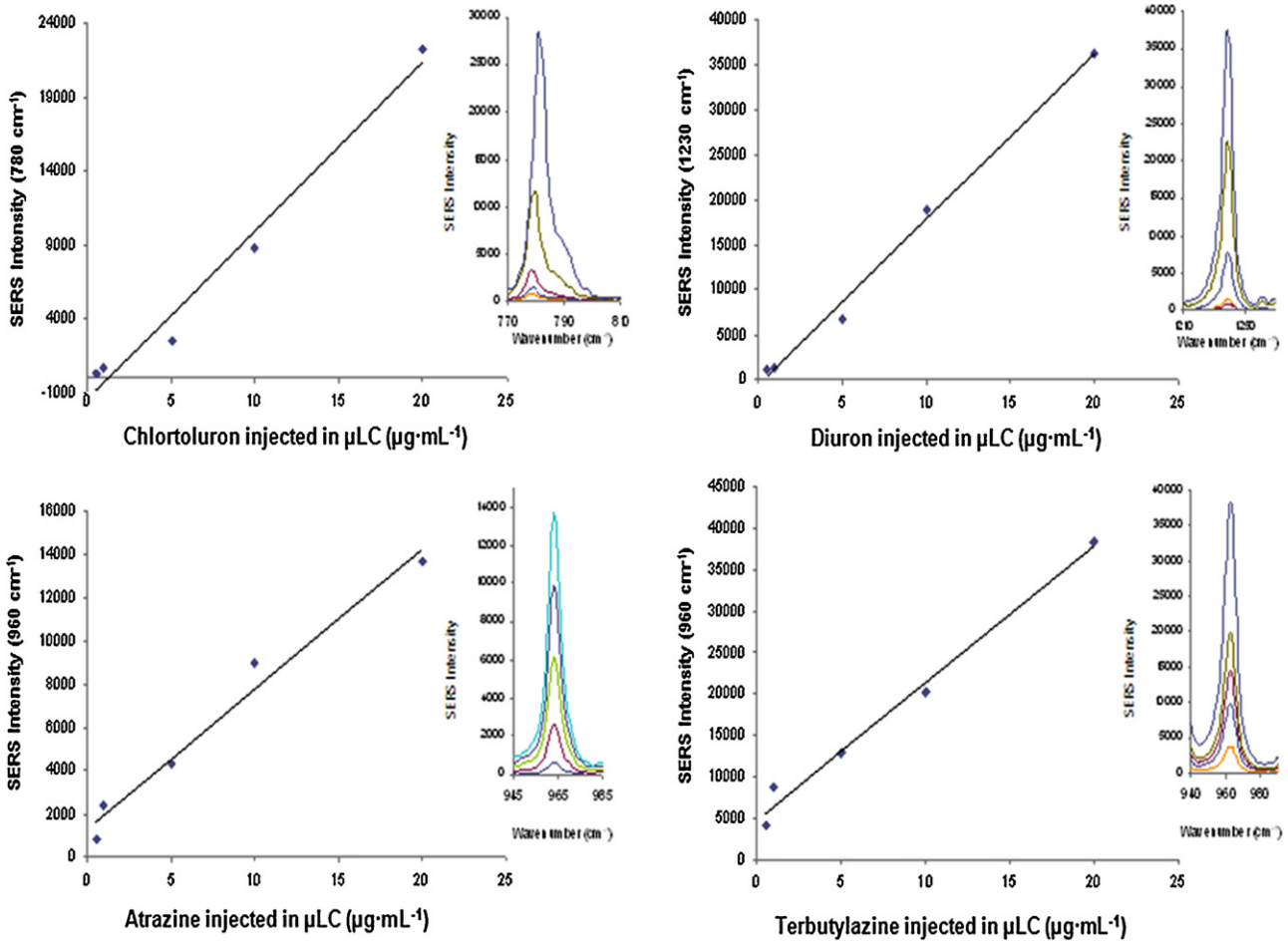

Fig. 4. Calibration of SERS spectra collected from spots of each analyte at different amounts injected in the µLC column (between 0.5 and 20 ng), plus the corresponding Raman peak used as analytical signal for each one.

can be seen the LOD achieved with the proposed methodology were much lower than those achieved by UV absorbance detection. It is important to note that the precision of the proposed method, in spite of the complexity of the interface, was slightly higher than those obtained with the UV spectrometer which is well known for its robustness. This increase in precision was attributed to the high compatibility of the microdispenser with a low flow stream coming from the capillary column versus other combinations, such as an LC system with a split flow interface, and the high reproducibility of the synthesis of the nanocomposite SERS substrate.

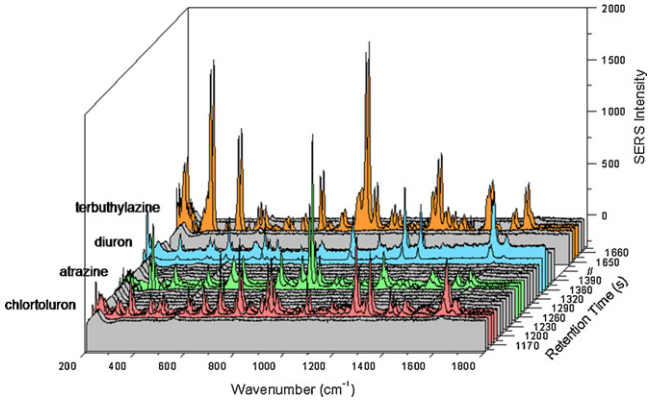

Fig. 5. 3D SERS chromatogram obtained from a 10 µg mL^{-1} pesticide mixture standard injected in the µLC column. The stops of the stage-dispersing unit were 10 s and the dispersing frequency of the microdispenser was 100 droplets per second.

In comparison with other similar capillary LC-(microdispenser)-FTIR combinations reported in literature [38] for the same compounds, the use of the nanocomposite has allowed the detection of as little as 0.2 ng of pesticides, amounts which are ten times lower than the amounts detected with other applications described in literature. The present gain in sensitivity is due to two reasons: the analyte spots produced by the microdispenser in the present work are considerably smaller, and thus more concentrated, than those obtained with the conditions used in the previous work [38], and also much better SERS detectability was achieved when using the novel colloidal Ag-QD solution as SERS substrate.

4. Conclusion

The combination of the µLC-(microdispenser)-SERS using a novel Ag-QD nanocomposite as a SERS-substrate was found to be a useful method for the separation, identification and quantification of pesticides. The detection limits achieved were very low, between ca. 10 and 20 pg deposited on the CaF_2 plate depending on the analyte selected. These were much lower than the detection limits achieved with UV absorbance detection, so that better quantitative and also qualitative (structural) information can be obtained with the methodology proposed in this paper. Considering these aspects together, and the high reproducibility of the system, it can be confirmed that the use of a microdispenser combined with the capillary LC and SERS detection using the nanocomposite are the

most reliable combination in order to obtain 3D chromatograms as well as the spectral information provided by enhanced Raman sensitivity.

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