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Optimization of SERS scattering by Ag-NPs-coated filter paper for quantification of nicotinamide in a cosmetic formulation

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ABSTRACT

Supported silver nanoparticles on filter paper were synthesized using Tollens' reagent. Experimental designs were performed to obtain the highest SERS enhancement factor by study of the influence of the parameters: filter paper pretreatment, type of filter paper, reactants concentration, reaction time and temperature. To this end, fractional factorial and central composite designs were used in order to optimize the synthesis for quantification of nicotinamide in the presence of excipients in a commercial sample of cosmetic. The values achieved for the optimal condition were 150 mM of ammonium hydroxide, 50 mM of silver nitrate, 500 mM of glucose, 8 min for the reaction time, 45 °C temperature, pretreatment with ammonium hydroxide and quantitative filter paper (1–2 μm). Despite the variation of SERS intensity, it was possible to use an adapted method of internal standard to obtain a calibration curve with good precision. The coefficient of determination of the linear fit was 0.97. The method proposed in this work was capable of quantifying nicotinamide on a commercial cosmetic gel, at low concentration levels, with a relative error of 1.06% compared to the HPLC. SERS spectroscopy presents faster analyses than HPLC, also complex sample preparation and large amount of reactants are not necessary.

1. Introduction

Raman spectroscopy has been widely used for pharmaceutical analysis in recent decades due to advances related to the development of electronics, optics and theoretical studies. It is a fast, non-destructive and non-invasive analytical technique [1] that provides a unique fingerprint spectrum and chemical information of several substances in any state of matter [2]. However, the low intensity of Raman signal causes limitations to its application due to the low sensitivity of this method [3]. Since the observation of Raman signal amplification due to the adsorption of molecules on metal surfaces, the surface enhanced Raman spectroscopy (SERS) has sparked intense research activity in several areas in recent years. Due to several advantages and investigation possibilities of the data given by the spectra, chemometric tools and refinement of the technique, SERS is becoming a useful analytical tool for detection and analysis of different molecules present in low concentration, even for detection of a single molecule under specific conditions [4]. SERS has proved to be an extremely effective technique in the study of drugs using several substrates, providing a rapid and increasingly precise quantification of their active ingredients [5]. SERS spectra are obtained by the adsorption of molecules on a roughened substrate surface as an electrode [6], metal colloids [7], films, metal foils [8], glass [9], filter paper [3,10–16], among others. In particular, the use of filter paper as the substrate for silver nanoparticles became attractive due to easy handling, low cost, fast manufacture, and no need to undertake a pre-processing of the sample [10].

Nicotinamide has been extensively studied in the context of Raman spectroscopy and it has been investigated by several techniques and computational methods. Raman spectra of nicotinamide, both in solid state and in aqueous solution, has already been reported in the literature at different pHs, but so far, few SERS studies have been conducted [17,18]. Nicotinamide (Fig. 1) or niacinamide is an amide of niacine (PP or B3 vitamin, nicotic acid) [18] and is an essential nutrient precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which reverse the symptoms of pellagra [19]. High doses of nicotinamide may be toxic in adults and in people with diabetes, asthma, liver diseases and ulcer [20], thus their identification is required even at low levels. Pal et. al [21] have already done a quantitative analysis of nicotinamide in vitamin tablets using the SERS technique with alumina coated silver nanoparticles and it was possible to quantify nicotinamide in low amounts (ppm) in commercial vitamin B_3 complexes. However, for the synthesis method

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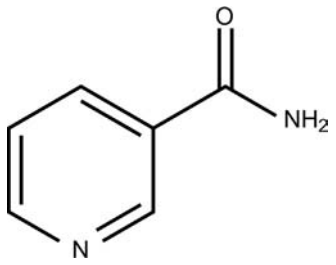

Fig. 1. Nicotinamide molecular structure.

and substrate proposed in this paper, a quantitative analysis of any analyte has not been reported in the literature. To detect low concentrations of molecules in aqueous solutions, it is necessary to significantly increase the SERS signal. For this, it is necessary to control the nanoparticle synthesis. Parameters such as temperature, reaction time and concentration of reactants significantly change the particle size, and thus change the intensity of the SERS signal.

An efficient nanoparticle synthesis can be improved by optimizing the parameters that influence the system, usually through screening experiments which identify the significant parameters that present great influence on the experimental response. The most commonly used method is the one-parameter at a time method, which consists of selecting a initial configuration for the experiment and then varying the value of only one parameter at a time, in a predefined range, keeping the others parameters constant [22]. However, the disadvantage of this method is the impossibility of studying the interaction between the parameters, which may lead to an incorrect combination choice of parameter values generating a response that may not be a global optimum. As this fact is unknown by most experimentalists, the method is used intensively [23].

To consider the interaction between the parameters, multivariate experimental designs need to be used. In these designs, the parameters are varied simultaneously, so that the possible combinations of the parameters are investigated, producing one or more responses of interest and avoiding incorrect conclusions. Sometimes the full factorial design cannot be applied due to the large number of experiments to be performed, and may not be useful because due to the required time and cost. In these cases the alternative is to use fractional experimental design, since it is not necessary to test all combination levels of the parameters to know which are most important. When system modeling is desired, there are situations where a linear model is no longer useful, thus, a quadratic model becomes necessary like the central composite design (CCD), which is one of the most used for modeling. Therefore, the goal of this work is to optimize the conditions of the synthesis of silver coated filter paper, aiming toward the highest increase in SERS signal response through experimental design, in order to obtain a new method to determine and quantify nicotinamide in commercial samples using an inexpensive, selective and simple analytical method.

2. Material and methods

2.1. Materials

All reagents used in the experiments were of analytical grade. Silver nitrate (Vetec 99.8%), glucose (Synth 99.9%) and ammonium hydroxide (Synth, 27%) were used for the syntheses of the nanoparticles. The solutions were prepared at room temperature in ultrapure water (18.2 M Ω cm) at concentrations according to the experimental designs. Nicotinamide was purchased from Aarti Drugs Ltd. and solutions of different concentrations were prepared in ultrapure water. The commercial sample was a gel with 40 mg per gram of nicotinamide. Each solution was freshly prepared before use.

2.2. Ag-NPs-coated filter paper preparation

Silver mirror reaction was used to prepare silver coated filter paper similar to that described in Cheng et al. [10]. The reactions were performed on an IKA heating plate, model C-MAG HS 7, with magnetic stirrer and electronic thermometer.

In a water bath, the solution of silver nitrate was added to a beaker. When the reaction temperature was reached, ammonium hydroxide was added to the solution yielding a brown precipitate, which was immediately dissolved and the solution became clear again. At the end, a glucose solution, previously heated to the reaction temperature, was added to the reaction followed by the immersion of the pre-treated filter paper, cut into 2 cm × 2 cm pieces, and positioned vertically into the beaker. The reaction media was stirred at 850 rpm to obtain a uniform coverage on the filter paper.

After the reaction time, the filter paper was removed from the beaker, rinsed with deionized water for 10 min and in methanol for 1 min, both in ultrasound. The paper was air-dried and immersed in nicotinamide solution of 10^{-3} mol L^{-1}. After 1 h, the paper was removed from the solution and allowed to dry for 20 min at 25 °C, and the spectra taken thereafter.

To obtain the maximum enhancement of the SERS signal, a 2_{IV}^{7-3} fractional factorial experimental design was performed with the most important variables in the nanoparticles synthesis, followed by a central composite design using the two more important parameters. In all analyses, the intensity value of the highest peak of the spectrum was used as response for the optimization.

2.3. Instrumental

Raman spectra were obtained using a Raman Spectrometer B&WTek Model BWS 415-785H managed by B&WSpec 3.27 software. The excitation wavelength was 785 nm, the integration time was 30 s, and laser power varying from 3.16 to 94.8 mW.

An HLPC-UV method, adapted from literature [24], was performed as the comparative method [24]. It was used an Agilent Technology 1200 Series HPLC, a Phenomenex Gemini C18 (150 mm × 4.6 mm, 5 μm) column, mobile phase acetonitrile:ammonium acetate buffer pH 5.0 (10:90), 20 min of run time, column temperature of 25 °C, detection at 254 nm and a flow rate of 0.8 mL min^{-1}.

2.4. Experimental designs

The parameters studied in the fractional factorial design were reactant concentrations, reaction time, temperature and type and pretreatment of the filter paper. Table 1 shows the values at the lower level, higher level and central point, which was conducted in triplicate using the values listed by Cheng et al. [10]

For each experiment 10 spectra were acquired and the two more intense and the two less intense spectra were neglected in order to minimize the differences associated to the high variability of the SERS signal on the surface of the silver NPs-coated filter paper. The averages of the six intensity values were calculated. Due to the variation in the filter paper color in each experiment of the experimental design, different laser powers were used for different experiments and the scattering intensity values were normalized to 31.6 mW (10% of total laser power).

The experiment with the highest SERS response was used as a central point for a new design, a CCD. Glucose and silver nitrate concentration were identified as significant parameter by the fractional factorial design and then studied in the new experimental

Table 1
Studied parameters of 2_{IV}^{7-3} fractional factorial design and its values on the high (+1) and low (−1) levels and on the central point (0).

Level	A	B	C	D	E	F	G
+1	75	450	750	8	65	H	K
0	50	300	500	6	55	I	L
−1	25	150	250	4	45	J	M

A: [$AgNO_3$] (mmol L^{-1}); B: [NH_4OH] (mmol L^{-1}); C: [$C_6H_{12}O_6$] (mmol L^{-1}); D: time (min); E: temperature (°C); F: pretreatment; G: filter paper; H: nitric acid; I: ammonium hydroxide; J: no pretreatment; K: quantitative (7–12 μm); L: qualitative (4–12 μm); M: quantitative (1–2 μm).

Table 2
Studied parameters of central composite design of two factors and the respective values of the levels (+1.41), (−1.41), (+1), (−1) and central point (0).

Level	[$AgNO_3$] (mmol L^{-1})	[$C_6H_{12}O_6$] (mmol L^{-1})
−1.41	39	396
−1	50	500
0	75	750
1	100	1000
1.41	110	1103

design. The others parameters were kept constant in the CCD at the same levels used in the best experiment of the fractional factorial design.

The values of the parameters at each level of the new design are listed in Table 2. The central point was carried out in triplicate and the parameter values of the best experiment obtained in the CCD were chosen to perform the nicotinamide quantification.

In this second design, there was just a little variation in the color of the paper in each experiment, thus the laser power of 3.16 mW (1% of the total laser power) was used in all analyses due to the dark gray color of the obtained silver NPs-coated filter paper.

2.5. Calibration curve

The calibration curve was carried out in triplicate, since the distribution of the nanoparticles on each piece of paper may not be uniform, and the concentration of nicotinamide solutions ranged from 1.0 mmol L^{-1} to 0.1 mmol L^{-1}. The obtained silver-coated filter paper was cut into six pieces and each of them was immersed in a solution of different concentrations of the calibration curve. After 1 h, the papers were removed and dried at 25 °C and 12 spectra of each paper were acquired, in different positions of their surfaces.

2.6. Commercial sample preparation for nicotinamide determination

The sample used to evaluate the developed SERS analytical method was a commercial cosmetic gel which presents 40 mg g^{-1} of nicotinamide and the excipients: glycerin, propylene glycol, carbomer, methylparaben, rosemary essential oil, ethyl alcohol and distilled water. For this, 76.5 mg of the gel sample was weighed and diluted with 10 mL of deionized water in a beaker. The solution was sonicated in an ultrasound for 30 min to completely dissolve the sample. The volume was completed to 25 mL in a volumetric flask and then diluted to a final nicotinamide concentration of 0.5 mmol L^{-1}.

3. Results and discussion

3.1. Fractional experimental design

Table 3 shows the data obtained from the spectrum of each experiment, the laser power, the average value of the scattering intensities at 1031 cm^{-1} and their normalized values for a laser power of 3.16 mW. Raman spectra of solid nicotinamide and SERS spectra of nicotinamide 1.0 mmol L^{-1} are illustrated in Fig. 2.

From the values of Table 3, a statistical analysis was performed in order to determine which parameters were more significant for increasing the SERS signal. Subsequently, the effect of the analyzed parameters and the interactions among them was determined. The importance of each parameter is proportional to their percentage of contribution among all other parameters, as shown in Fig. 3.

In order to optimize the SERS effect, we chose the two parameters which presented the highest effects. It can be observed in Fig. 3 that the concentration of glucose, silver nitrate and the

Table 3
Fractional factorial design results and the laser power used in each experiment, average and normalized intentsity.

Experiment	A	B	C	D	E	F	G	Laser power (mW)	Normalized intensity (u.a.)
CP 1	0	0	0	0	0	0	0	15.8	558
CP 2	0	0	0	0	0	0	0	15.8	316
CP 3	0	0	0	0	0	0	0	15.8	384
1	−1	−1	−1	−1	−1	−1	−1	94.8	29
2	−1	−1	−1	+1	+1	+1	+1	63.2	7
3	−1	−1	+1	−1	+1	+1	−1	31.6	2169
4	−1	−1	+1	+1	−1	−1	+1	3.16	6676
5	−1	+1	−1	−1	+1	−1	+1	47.4	219
6	−1	+1	−1	+1	−1	+1	−1	63.2	14
7	−1	+1	+1	−1	−1	−1	+1	63.2	3
8	−1	+1	+1	+1	+1	−1	−1	3.16	4284
9	+1	−1	−1	−1	−1	+1	+1	15.8	99
10	+1	−1	−1	+1	+1	−1	−1	15.8	204
11	+1	−1	+1	−1	+1	−1	+1	3.16	14,311
12	+1	−1	+1	+1	−1	+1	−1	3.16	16,706
13	+1	+1	−1	−1	+1	+1	−1	31.6	89
14	+1	+1	−1	+1	−1	−1	+1	15.8	881
15	+1	+1	+1	−1	−1	−1	−1	15.8	1220
16	+1	+1	+1	+1	+1	+1	+1	3.16	13,699

CP: central point, A: [$AgNO_3$] (mmol L^{-1}), B: [NH_4OH] (mmol L^{-1}), C: [$C_6H_{12}O_6$] (mmol L^{-1}), D: time (min), E: temperature (°C), F: pretreatment, G: filter paper.

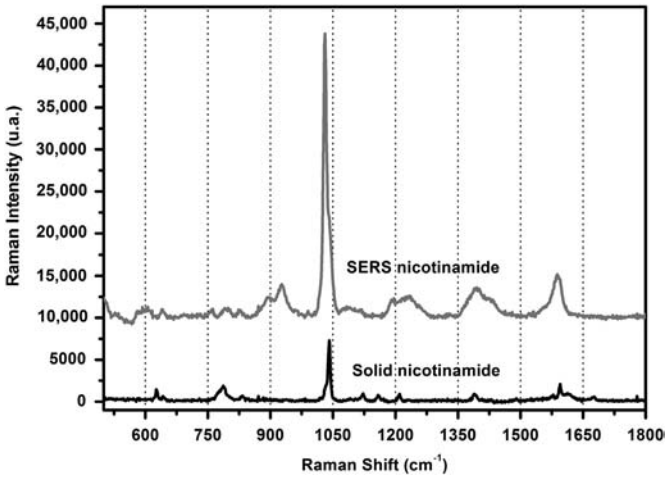

Fig. 2. Raman spectrum of solid nicotinamide (black line) and SERS spectrum of nicotinamide 1 mmol L^{-1} (gray line).

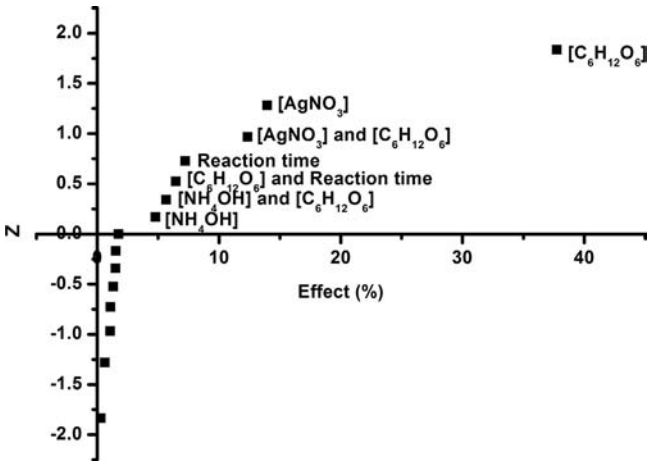

Fig. 3. Normal probability plot for the fractional factorial design.

Table 4
Central composite design results containing the average value of the scattering intensity using a laser power of 3.16 mW.

Experiment	Level		Mean value of Raman intensity (u.a.)
	$[AgNO_3]$ (mmol L^{-1})	$[C_6H_{12}O_6]$ (mmol L^{-1})	
CP 1	0	0	19,222
CP 2	0	0	21,699
CP 3	0	0	16,283
1	−1	−1	26,129
2	−1	1	21,008
3	1	−1	11,263
4	1	1	19,558
5	−1.41	0	22,235
6	1.41	0	19,817
7	0	−1.41	15,953
8	0	1.41	21,228

CP: central point.

interaction between them were the most significant parameters that enhanced the SERS signal. Thus, a central composite design of the two parameters was developed using the concentration of these two reactants as variables. The remaining parameters were kept constant under the conditions of the best factorial fractional design experiment, which was experiment 12: 8 min of reaction time; ammonium hydroxide 150 mmol L^{-1}; reaction temperature of 45 °C; and quantitative filter paper (1–2 μm) pretreated with 10% v/v ammonium hydroxide.

3.2. Central composite design (CCD)

The results for each experiment are shown in Table 4. It was observed that the best result was obtained in the experiment 1.

A quadratic model was proposed for this system; however the quadratic equation could explain only 61% of the variance of the model. In addition, the values obtained by the F test to verify the lack of fit and the F test of the regression model indicate that the model presented lack of fit and the regression could not be used to prediction.

Therefore, the values obtained by the central composite design were used to estimate an empirical response surface by interpolation (the octagon in the Fig. 4), instead of using the equation proposed by the design. The empirical responses in the Fig. 4 show clearly that a second order equation cannot explain such surface, because the responses are almost constant when glucose concentration is equal or higher than 750 mM and there are great changes

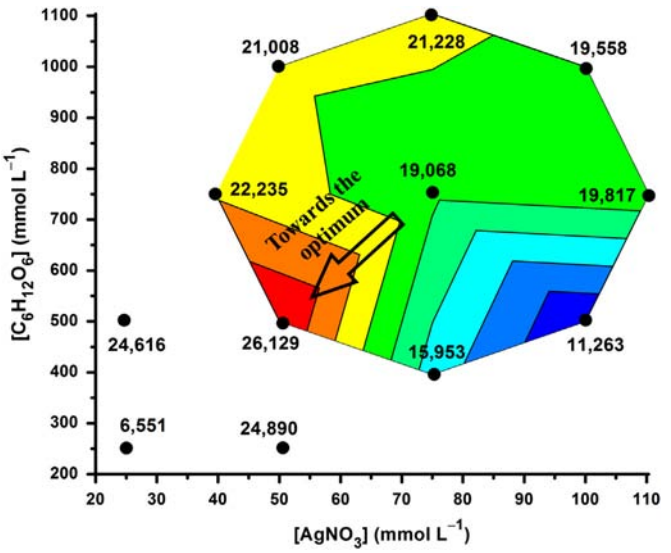

Fig. 4. Response surface of the central composite design using empirical values of Raman scattering intensity at 1031 cm^{-1}.

in the Raman scattering when glucose concentration is lower than 750 mM. However, even if it was not possible to estimate a quadratic model for this system, it was possible to obtain an optimal experimental condition when the SERS effect presented the highest value within the studied experimental domain, in this case, silver nitrate concentration 50 mmol L^{-1} and glucose concentration 500 mmol L^{-1}. In order to verify if the condition using silver nitrate 50 mmol L^{-1} and glucose 500 mmol L^{-1} was really close to the optimum of the experiment, three new experiments were performed toward the optimum, as shown in Fig. 4. However, none of them presented better results than the best condition found in the CCD.

The central point of the fractional experimental design, where we began the pursuit for a better SERS signal, presented average scattering intensity of 419, when normalized to the laser power 36.1 mW. The optimum achieved by the CCD presented a scattering intensity of 26,129 using just 3.16 mW of laser power (10 times lesser). Then, the total increase in SERS signal achieved by the optimization was around 624 times.

Therefore, this optimal condition was used to build the calibration curve and to predict the nicotinamide content in the sample: silver nitrate 50 mmol L^{-1}; glucose 500 mmol L^{-1}; ammonium hydroxide 150 mmol L^{-1}; 8 min of reaction time; reaction temperature of 45 °C; using quantitative filter paper (1–2 μm) pretreated with ammonium hydroxide 10% v/v.

3.3. Characterization of the Ag-NPs-coated filter paper

A micrograph of the raw filter paper (Fig. 5a) and micrographs of the Ag-NPs-coated filter paper (Fig. 5b and c) produced under the optimal experimental condition was obtained using a scanning electronic microscopy (Philips XL-30 FEG). Fig. 5b shows thousands of Ag-NPs supported on a cellulose fiber, and Fig. 5c presents a higher magnification, where particles smaller than 100 nm can be seen. The particle size distribution of the silver nanoparticles was 94–275 nm for 95% of the particles with an average size of 180 nm.

The X-ray diffraction pattern of the Ag-NPs-coated filter paper was recorded on a Shimadzu XRD 6000 diffractometer using Cu radiation operated at 30 kV, 30 mA and 2.0 (deg/min). The experiment was performed in the diffraction angle range of 30–80° 2θ. Fig. 6a presents the diffractogram of the silver nanoparticles on the

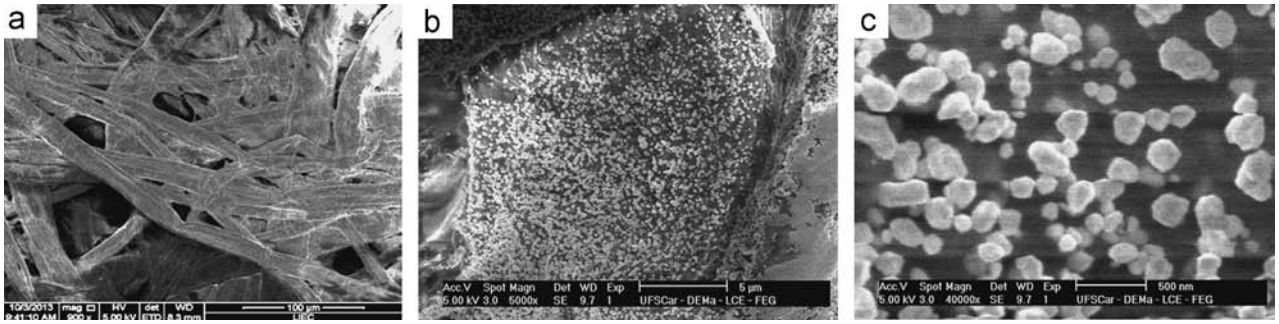

Fig. 5. Micrograph of the raw filter paper (a) and micrograph of Ag-NPs-coated filter paper produced under the optimal experimental condition: (b) 5000 × of magnification and (c) 40,000 × of magnification.

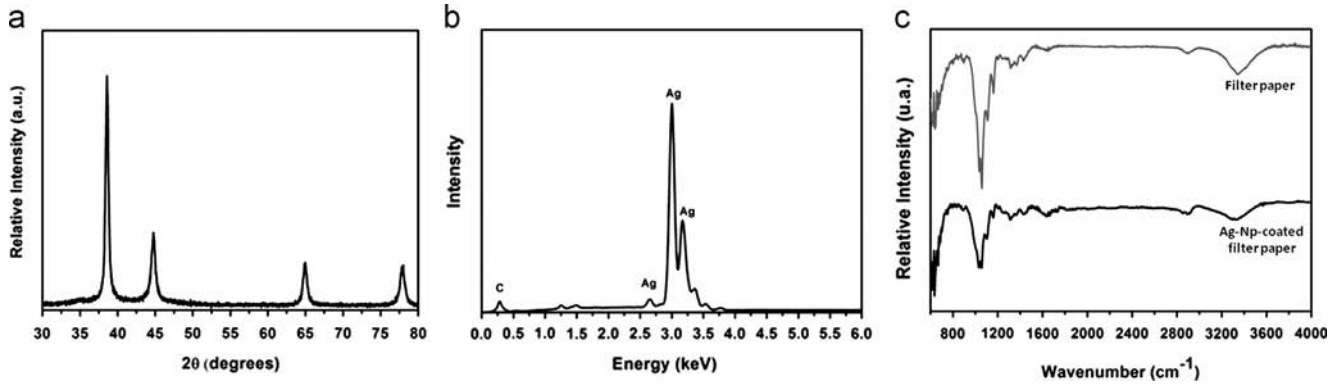

Fig. 6. Characterization of the Ag-NPs-coated filter paper produced under the optimal experimental condition: (a) XRD, (b) EDS and (c) FT-IR.

filter paper. Four distinct diffraction peaks are observed at 2θ values of 38.3°, 44.4°, 64.9° and 77.9°, corresponding to the (111), (200), (220) and (311) crystalline planes of cubic Ag [25,26].

Fig. 6b presents the energy-dispersive X-ray spectrum (EDS). It can be observed that only silver nanoparticles were deposited on the surface of the filter paper, and it was not evidenced the presence of silver oxide.

Fig. 6c shows the mid-infrared spectra obtained using the attenuated total reflectance accessory (FT-ATR-IR) for the raw filter paper and the silver-coated filter-paper. It can be observed that there are no different peaks between them, and those which appears in the spectra come from cellulose. The intensity of the peaks is not similar due to the deposition of silver nanoparticles on the surface of filter-paper that hinders the evanescence radiation to interact with cellulose. As expected, there are no peaks from silver nanoparticles, since they are not active at the mid-infrared.

3.4. Calibration curve for nicotinamide quantification

An analytical curve was developed to quantify nicotinamide using standard concentrations within a range of 0.1–1.0 mmol L^{-1} (or 12.1–121.2 ppm). For a greater representativeness of the filter paper, 12 spectra were taken for each standard concentration. An average with the 12 spectra of each concentration was made and this average was normalized by the intensity of the spectra of highest concentration (Fig. 7). The calibration curve (Fig. 8) and quantification of the sample was made in triplicate at different days.

For the quantification of the commercial sample, the substrate was cut into six pieces, and three pieces were immersed in the sample solution and the other three in the standard solution of concentration 1.0 mmol L^{-1} in order to normalize the intensity of the scattering of the sample by the more concentrated standard. The filter papers were immersed in random order. The nicotinamide concentration found in the commercial sample was 40.71 ± 0.92 mg g^{-1}. The concentration obtained by the reference method

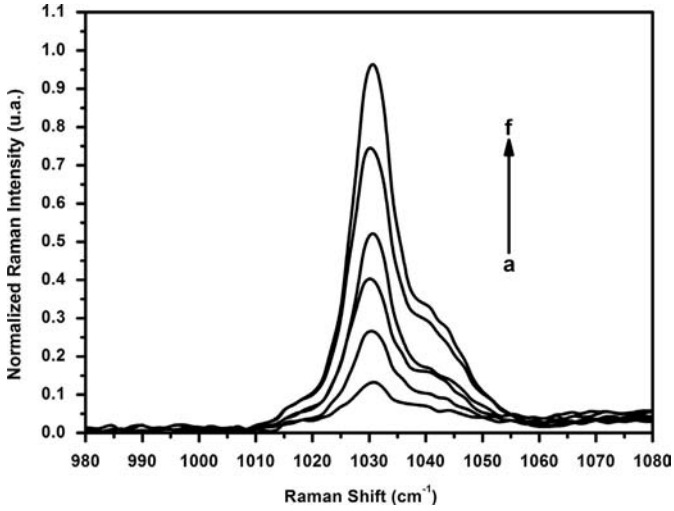

Fig. 7. SERS spectra of nicotinamide in different concentrations: (a) 0.1 mmol L^{-1}, (b) 0.2 mmol L^{-1}, (c) 0.4 mmol L^{-1}, (d) 0.6 mmol L^{-1}, (e) 0.8 mmol L^{-1} and (f) 1 mmol L^{-1}.

(HPLC) was 40.28 ± 0.56 mg g^{-1}. The proposed method showed a relative error of 1.06% compared with the reference method used. A Student's t-test at confidence level of 95% revealed no significant statistical difference between SERS and HPLC methods for nicotinamide quantification at the analyzed sample (t_{calc}=0.691 and $t_{value,\ 4\ d.f.,\ 95\%}$=2.262).

Fig. 9 shows Raman spectra of the cosmetic sample with an incident laser power of 316 mW (100 times higher than used in the SERS analyses) and SERS of the same cosmetic sample diluted approximately 655 times (to obtain nicotinamide concentration 0.5 mmol L^{-1}) with an incident laser power of 3.16 mW, both with an integration time of 30 s. It can be observed that the commercial sample with and without SERS present the characteristic peak of

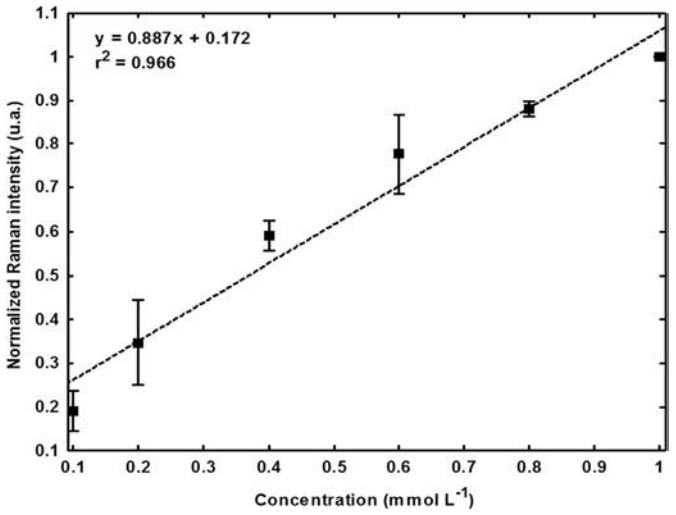

Fig. 8. Calibration curve for nicotinamide quantification in the sample.

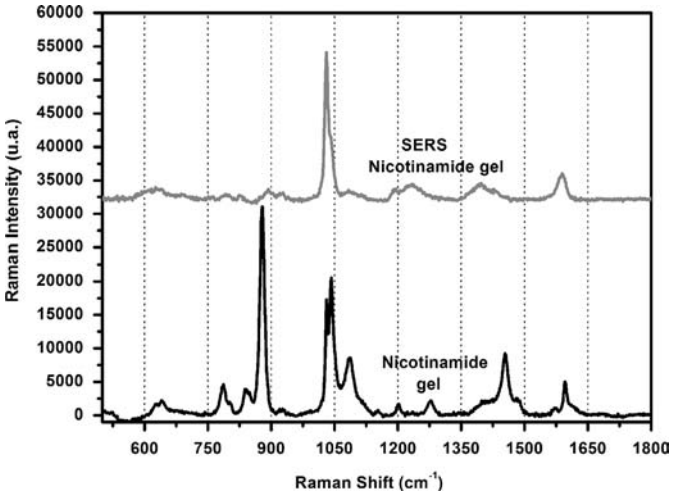

Fig. 9. Raman spectrum of nicotinamide gel sample (black line) and SERS spectrum of nicotinamide gel 0.5 mmol L^{-1} (gray line).

nicotinamide at 1031 cm^{-1}, which means that only the nicotinamide molecule is significantly adsorbed on the Ag-NP surface and the analytical method presents high selectivity for the analyte. When the laser power and the dilution factor are taken into account in the Fig. 9, we can find an increase in the Raman scattering around 70,000 times higher when SERS is employed.

4. Conclusions

It was possible to optimize the synthesis of silver nanoparticles on filter paper using two experimental designs to enhance the SERS signal. The scattering obtained using the optimal synthesis was around 624 times higher than the initial experimental condition, and around 70,000 times higher than traditional Raman analysis. Unlike the traditional Raman spectrum of the commercial sample, the SERS was selective for the analyte, allowing the use of the univariate calibration.

Although there was a small variation of the SERS scattering signal, it was possible to use an adapted method of internal standard to construct a calibration curve and thus, achieve better reproducibility in the obtained data.

The method proposed in this work was capable of quantifying nicotinamide at low concentration levels with a relative error of 1.06% compared to the HPLC method. The SERS technique is shown to be a powerful tool to develop faster, cheaper and greener analytical methods than traditional ones, since the sample preparation is simple and just a small amount of reactants is used.

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