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Redox titration on foldable paper-based analytical devices for the visual determination of alcohol content in whiskey samples

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ABSTRACT

This report describes the development of foldable paper-based analytical devices (PADs) to perform redox titrations. Paper devices were designed to contain three spot tests, which were wax printed and folded to create a three-layer structured platform and to promote the sample transport based on vertical flow. The proposed devices were explored for the visual determination of the alcoholic content in whiskey samples. For this purpose, a classical permanganometry reaction was employed to allow the indirect determination of ethanol based on the required amount of oxalic acid to react with the excess of permanganate in acidic medium. The endpoint of the redox titrations performed in different alcoholic concentrations was measured and revealed a good linear behavior for the ethanol concentration range between 0% and 50% (R^2 = 0.992), achieving a limit of detection equal to 2.1%. The alcoholic content was determined in a total of 44 whiskey samples seized by the Brazilian Federal Police. When compared to genuine samples and using an established cut-off limit, 73% of the seized samples were correctly classified as whiskeys containing adulterated alcoholic content. The proposed method was compared to a reference protocol and no difference was observed at the confidence level of 95%. The instrumental simplicity, the low cost, the sample volume requirement, the short analysis time and mainly the inherent portability make these devices quite attractive for on-site forensic applications.

1. Introduction

In the last decade, portable and inexpensive analytical platforms have emerged as powerful alternative tools for forensic applications directly at the point-of-need (PON) [1]. Recent examples including the detection of gunshot residues [2], chemical and biological warfare agents [3], forensic genotyping [4], post-mortem interval [5], blood analysis [6], gemstone and minerals [7,8], drugs [9–12], explosives [13–17] and beverages adulterations [18–20] have been reported exploiting portable analytical platforms.

The adulteration of alcoholic beverages has been a common practice aiming to increase the profit by malicious organizations [1]. Due to the high market value, whiskey has been one of the favorite beverages to be adulterated [19,21]. In general, the falsification occurs through the dilution with water or cheaper alcoholic beverages as well as through the addition of dyes or colored drinks [22,23]. Conventional techniques including chromatography [21], capillary electrophoresis [24], mass spectrometry [25], electrochemistry [26] and near-infrared spectroscopy [27,28] have been extensively employed to identify these adulterations.

Different analytical methodologies employing portable devices have been successfully developed to promote a fast screening of the whiskey authenticity. Rezende et al. demonstrated the use of microchip electrophoresis devices integrated with contactless conductivity detection for a rapid screening of the anionic profile of the whiskey samples seized by the Brazilian Federal Police [18]. The authors reported that fluoride and chloride ions are two target anions with great potential to correctly classify and distinguish adulterated whiskeys from genuine whiskeys. Cardoso and co-workers reported the use of wax printed paper spot tests to detect caramel dye in seized whiskey samples [19]. Tosato et al. showed that the adulteration of whiskey with sugar cane spirit can be easily identified using paper spray ionization mass spectrometry devices [20].

In the last five years, microfluidic paper-based analytical devices (μPADs) have demonstrated great ability to be used in forensic

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applications, as recently covered in a review article [1]. The advantages associated with low cost, global affordability of paper substrates, biocompatibility and mainly the versatility to allow the fabrication of spot tests [29], lateral flow devices [30,31], two-dimensional [32,33] and three-dimensional μPADs [34,35] are some attractive features that candidate paper as potential platform for on-site forensic analysis.

Volumetric titrations involving acid-base, complexation and redox reactions were recently demonstrated on paper platforms by different authors. Karita and Kaneta developed μPADs containing an array of ten reservoirs interconnected by microfluidic channels for performing acid-base and complexometric titrations [36,37]. In 2014, the authors successfully showed the proof-of-concept using classical acid-base titrations to determine the acidity of hot spring water [36]. For complexometric titrations using ethylenediaminetetraacetic acid as chelating agent, the Ca and Mg concentrations were determined in mineral, river and sea water samples [37]. In both examples, the titration endpoint was determined by naked eye. Our group reported another study showing the use of a free application (PhotoMetrix®) to monitor acid-base titrations on wax printed spot tests based on color intensity measurements [38]. The proposed approach was able to establish a good correlation between the pixel intensity of the resulting color and the pH values of solutions prepared with a natural indicator. Myer et al. described an iodometric titration on a printed card. Color intensity was captured through a scanner and analyzed in a graphic software [39]. The back-titration procedure proposed by the authors was successfully explored to detect amoxicillin.

In this current study, we propose the development of foldable PADs to perform redox titrations aiming the visual determination of the alcoholic content in genuine and adulterated whiskey samples. For this purpose, PADs were structured in three layers to promote the sample transport based on vertical flow. The analytical performance was thoroughly investigated including the linear concentration range, selectivity, stability, detectability and the reliability. The forensic feasibility of the proposed devices was demonstrated through the analysis of seized whiskey samples.

2. Materials and methods

2.1. Chemicals and materials

Potassium permanganate (Synth, Diadema, São Paulo, Brazil), sodium oxalate (Vetec, Duque de Caxias, Rio de Janeiro, Brazil), ethanol (Vetec, Duque de Caxias, Rio de Janeiro, Brazil), sulfuric acid (Neon, Suzano, São Paulo, Brazil) were analytical grade and used as received without further purification. Stock solutions were prepared daily using ultrapure water (resistivity equal to 18.2 MΩ cm) processed through a purification system (Direct-Q®3, Millipore, Darmstadt, Germany). Filter paper model JP40 was obtained from Quanty (São José dos Pinhais, Paraná, Brazil).

2.2. Fabrication of foldable paper-based analytical devices (PADs)

Paper-based analytical devices were fabricated by wax printing [40]. Briefly, the device layout was drawn in the Corel Draw software, printed on paper surface using a wax printer (Xerox ColorQube 8570, Xerox Corporation, Rochester, NY, USA) and heated at 150 °C during 60 s to melt the wax and promote the creation of hydrophobic barriers. The device layout was designed to contain three microzones (diameter of 6 mm each) for (i) detection, (ii) reaction and (iii) titrant addition, as displayed in Fig. 1a. After printing and heating, detection and titrant addition zones were turned over the reaction zone in 180 degrees in the clockwise and counterclockwise (Fig. 1b), respectively, to align all zones together and to create a three-layer structure device. The multilayer PAD was stapled to ensure the sample transport through vertical flow.

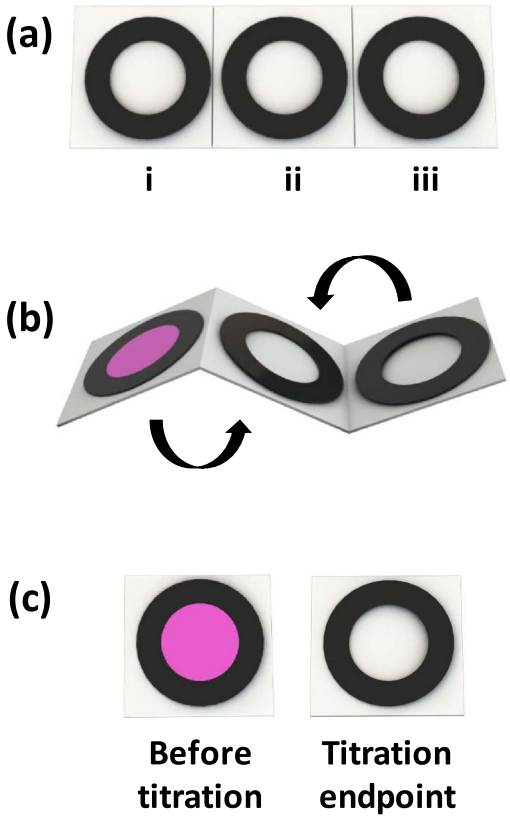

Fig. 1. Layout of the foldable paper-based analytical device (a) after wax printing and (b) during folding. In (a), the labels (i), (ii) and (iii) indicate the spots for sampling, reaction and detection, respectively.

2.3. Redox titrations on foldable PADs

Initially, the desirable reagents were added in the spots using a manual micropipette before the folding step. Aliquots of 3 μL and 1 μL of 0.02 mol L^{-1} $KMnO_4$ and 0.2 mol L^{-1} H_2SO_4 solutions were spotted in the detection (i) and reaction (ii) zones, respectively. Then, 1 μL of sample or standard ethanol solution was pipetted in the detection spot. Afterwards, the three layers of paper were aligned, and the bottom layer (detection zone) was sealed with adhesive tape to avoid solution leakage. For the redox titration, 0.5 μL aliquots of 0.05 mol L^{-1} $Na_2C_2O_4$ were added in the titration addition zone.

2.4. Visual detection

The titration endpoint was detected by naked eye, thus eliminating the use of any instrument for measuring the color intensity. The titrant volume required to reach the titration endpoint was used to determine the alcoholic content in whiskey samples.

2.5. Whiskey samples

The feasibility of the proposed device for forensic screening was tested with a total of 44 samples of whiskey seized by the Brazilian Federal Police. All seized samples were identified with labels from Ballantines (BL) (13 samples), Natu Nobilis (NN) (17 samples) and Red Label (RL) (14 samples) brands. In addition, genuine samples from the same labeled brands were also analyzed in the proposed devices to compare the concentration values of alcoholic content. Redox titration on foldable PAD was performed without any pretreatment or dilution of the whiskey samples.

2.6. Reference method

To verify the reliability of the proposed method, eight standard solutions of ethanol prepared at the concentration range between 10% and 50% (v/v) were analyzed by the proposed and reference methods. The analysis through the official method was carried out in a national laboratory supported by the Ministry of Agriculture, Livestock and Supply, located in Goiânia, Goias, Brazil. The official method was based on density measurements employing an automatic density meter (model DDM 2911 plus, Rudolph Research Analytical). The densimetric measurements were preceded by a distillation step to avoid false results due to the presence of sugars and other solutes present in the whiskey samples. The results obtained by both methodologies were statistically compared through the t-student test [41] at a confidence level of 95%.

3. Results and discussion

Paper-based platforms have successfully demonstrated their huge capacity for forensic applications and great ability to be used in the point-of-need with minimal or none instrumentation [1]. In our study, PADs were created containing three wax printed spot tests that were subsequently folded to allow the solution transport through vertical flow. During the fabrication protocol, the diameter of the spot tests was studied in a range between 2 and 10 mm. Smaller spots were not considered due to the blocking with wax particles, previously observed in other study [38].

Considering the aliquots added in each layer, the spot tests defined with diameters between 2 and 5 mm revealed solution leakage over the wax barriers (data not shown). In addition, in the devices designed with these dimensions, the titration was considerably very fast making difficult the visualization of the endpoint. The best analytical response was achieved when the spot test was printed with 6 mm diameter. For spots defined with diameter larger than 6 mm, the color distribution did not present good uniformity and analytical reliability to proceed with the titrations. For this reason, the diameter of 6 mm was selected as optimum and kept constant for all the subsequent experiments performed in this study.

3.1. Redox titration on foldable PADs and optimization of analysis conditions

The redox titration on paper occurs in two steps, as can be seen in reactions 1 and 2. First, the permanganate oxidizes the alcohol present in the sample under acidic medium (see Reaction 1). Subsequently, the excess of the permanganate, which did not react with the alcohol, oxidizes the oxalic acid leading to the formation of carbon dioxide, water and manganese ion (see Reaction 2). In this case, the ethanol concentration is indirectly determined based on the amount of oxalic acid consumed during the back-titration and considering the stoichiometric ratio. Consequently, the magenta color initially seen due to the presence of permanganate solution gradually changes to colorless, thus indicating the titration endpoint.

$$5\ CH_3CH_2OH + 2\ MnO_4^- + 6H^+ \rightarrow 5\ CH_3COOH + 2\ Mn^{2+} + 3H_2O \quad \text{(Reaction 1)}$$

$$2\ MnO_4^- + 5C_2O_4^{2-} + 16H^+ \rightarrow 2\ Mn^{2+} + 10\ CO_2 + 8H_2O \quad \text{(Reaction 2)}$$

Before performing redox titrations on paper, the sulfuric acid concentration required to promote the oxidation of alcohol by permanganate was optimized. Sulfuric acid solutions with concentrations between 0.1 and 1 mol L^{-1} were then tested (in increments of 0.1 mol L^{-1}) and the resulting optical images are displayed in Fig. 2. For concentrations greater than 0.3 mol L^{-1}, paper was burned creating holes in the surface, as expected. When the H_2SO_4 concentration varied from 0.1 to 0.3 mol L^{-1}, no noticeable change in the paper surface was visually observed. For the redox reaction, the concentration of 0.1 mol L^{-1} was not enough to ensure the oxidation of alcohol since no color change was observed. On the other hand, color changes were similarly seen when sulfuric acid was used at concentrations of 0.2 and 0.3 mol L^{-1}. Therefore, the 0.2 mol L^{-1} H_2SO_4 solution was selected as optimum for the subsequent experiments.

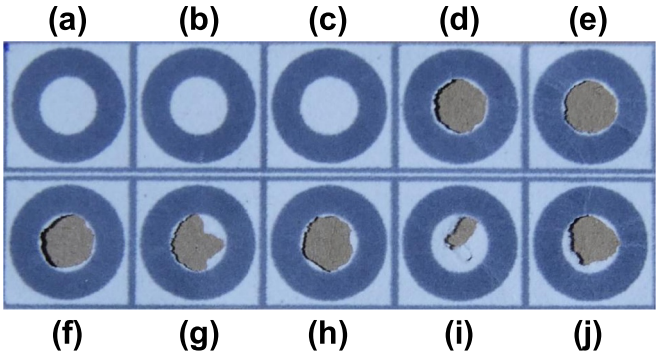

Fig. 2. Optical image showing the paper spot tests after adding of H_2SO_4 solutions prepared in concentrations from 0.1 to 1.0 mol L^{-1} using increments of 0.1 mol L^{-1} (a-j). The spot test array was fixed on a brown paperboard surface to make clear the holes in the paper surface.

The stability of the MnO_4^- solution previously spotted in the foldable PADs was also investigated. Basically, several PADs were prepared as described in Section 2.3 and used for redox titrations (keeping ethanol concentration fixed at 40%) in different times after spotting reagents. As can be noted in Fig. S-1 (available in electronic supplementary material, ESM), the volume required to reach the titration endpoint did not change from 0 to 40 min. On the other hand, when the titration was performed after 50 min, the volume decreased to ca. 10 µL. In a similar way, the volume required to reach the endpoint was 9 µL for a period between 120 and 360 min, i.e., during 4 h. Although the stability observed after 120 min is longer than the initial period, the precision of the endpoint measurement is affected due to the low color intensity. Then, the results presented in Fig. S-1 suggest that the stability of the proposed device is limited to 40 min. This time is enough to perform a complete redox titration and it does not compromise the analytical performance.

3.2. Selectivity of the redox titration

The reaction selected to evaluate the alcoholic content promotes color changes for primary and secondary alcohols. In this case, the presence of other alcoholic compounds in the sample may affect the colorimetric response on foldable PADs. The selectivity was then studied to evaluate the effect of a binary mixture containing ethanol and methanol on the analytical response. First, the ratio between ethanol and methanol was ranged keeping constant the amount of water at 50%. As can be seen Fig. 3a, the titrant volume required to reach the back-titration endpoint exhibited average valor equal to 11.7 ± 0.2 µL. This behavior suggests that the binary composition, with alcoholic content of 50%, did not affect the volume required to reach the endpoint during the back-titration.

Additionally, the alcoholic content was changed by raising the methanol percentage from 0% to 50% (v/v) keeping constant ethanol at

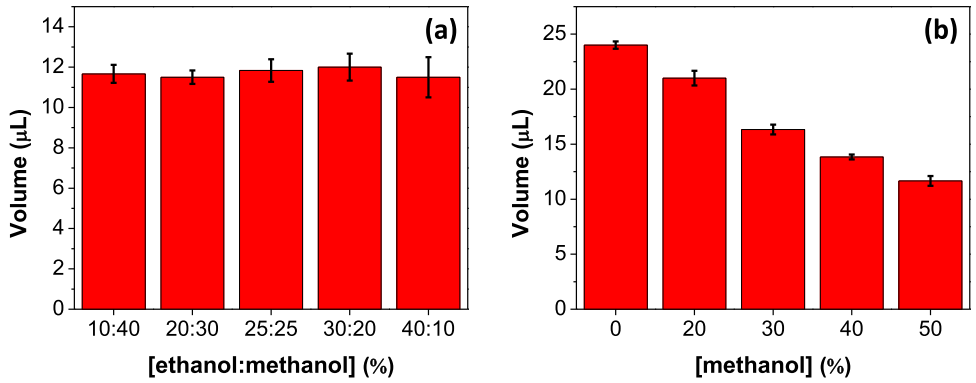

Fig. 3. Effect of the (A) ethanol: methanol ratio and (B) methanol concentration levels on the required volume to reach the back-titration endpoint on foldable paper-based devices. In (B), the ethanol concentration was kept constant at 50% (v: v).

50% (v/v). As displayed in Fig. 3b, the volume required to reach the titration endpoint decreased inversely proportional to the alcoholic content. When the methanol concentration increased from 0% to 50% (v/v), the average volume to complete the back-titration decreased from 24.0 ± 0.3 to 11.7 ± 0.4 μL. This was somehow expected since the larger amount of alcohol consumes greater quantity of permanganate. In this case, the excess of permanganate is noticeably reduced to react with oxalic acid, thus justifying the behavior presented in Fig. 3b.

Considering the results achieved and depicted in Fig. 3, it is clear that the proposed device is not selective for ethanol but rather for the alcohol content. However, methanol is toxic and it may promote severe and even fatal illness [42]. When compared to ethanol, methanol is more expensive and needs to be imported becoming unlikely its use to adulterate whiskey in Brazil. For this reason, we assumed that the alcoholic content depends mostly on the ethanol concentration.

3.3. Analytical performance

The analytical performance of the redox titration on foldable PADs was investigated aiming to detect the alcohol content in seized whiskey samples. For this purpose, the effect of the ethanol concentration on the consumed volume during the titration was initially tested. As can be noted in Fig. 4, the titrant volume required to reach the titration endpoint was inversely proportional to the ethanol concentration. This was somehow expected once the consumed volume of titrant refers to the amount required to react with the excess of permanganate. A linear behavior (correlation coefficient equal to 0.992) was observed when the ethanol concentration ranged from 0% to 50% (v/v).

In the data presented in Fig. 4, each point means the average value of five measurements while the error bar indicates the standard deviation. It is important to note that the relative standard deviation

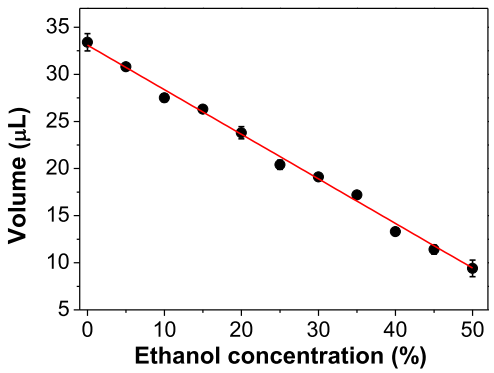

Fig. 4. Calibration curve for ethanol using foldable paper-based analytical devices and visual detection.

(RSD) values ranged from 0.8% to 9.4%. The highest RSD values were observed when the ethanol concentrations were equal to 0% and 50%. For the lowest concentration of ethanol, it was observed the generation of a noticeable color gradient caused most probably by the excess and leakage of solution through barriers. The lack of color homogeneity in the spot compromised the repeatability. On the other hand, the high RSD found for the 50% ethanol solution is justified by the difficulty to visualize the titration endpoint, since the reaction is rapid and requires low volume amount.

Considering the analytical curve presented in Fig. 4, the limit of detection (LOD) and the limit of quantification (LOQ) values for ethanol were calculated and the achieved values were 2.1% and 7.1%, respectively. The LOD achieved using foldable PADs was compared to the values described in the literature. The detectability level herein reported is higher than those determined by nuclear magnetic resonance [43], spectrophotometry [44], near-infrared and Raman spectroscopy [45,46], electrochemical biosensors [47,48], flow injection analysis connected with a charge coupled device [49] as well as gas chromatography with flame induced detector [50].

Most of the methodologies described in the literature provide excellent detectability levels and are widely explored for quantitative purposes. However, some techniques require sophisticated instrumentation, laborious sample pretreatment procedures as well as users with technical skills. On the other hand, the use of foldable PADs offers operational simplicity, portability and low cost. Furthermore, the determination of ethanol through redox titrations on the proposed PADs allows response in short time, requires low sample consumption, generates negligible amount of waste and enables the visual detection, i.e., without any electronic device for the image capture.

On this basis, it can be inferred that the detectability levels achieved using foldable PADs and visual detection are enough to allow the quantitative determination of the alcoholic content in samples of whiskey, which genuinely presents a concentration between 38% and 43% (v/v). In this way, the proposed devices were explored for the quantitative analysis of different samples seized by the Brazilian Federal Police. The accuracy of the method was investigated through a comparison with a reference method.

3.4. Comparison with a reference method

The reliability of the redox titration performed on the foldable PADs was compared to the reference method, which employs a digital electronic densitometer. For this purpose, eight standard solutions of ethanol were prepared in the concentration range between 10% and 50% (v/v) and analyzed by both methods. The correlation for the alcohol content achieved by the proposed method versus the reference method is depicted in Fig. 5 and presented coefficient of correlation equal to 0.994.

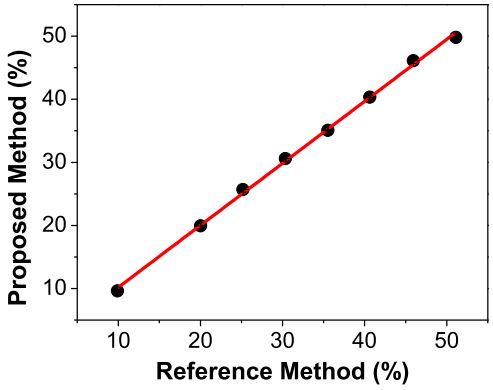

Fig. 5. Comparison of the ethanol concentration achieved in eight standard solutions using by using foldable PADs (proposed method) and densitometer measurements (reference method).

The statistical comparison of the data achieved by using foldable PADs and reference method was performed by F-test and T-test, at a confidence level of 95% in both cases. For the F-test, the calculated value for all samples was greater than the critical F-test value (F_{crit} = 6.388), thus indicating that the reference method has precision greater than the proposed method. On the other hand, the calculated T-test values for all the samples were lower than the critical T-test value (t_c = 2.306), allowing to infer that the data found by the foldable PADs and densitometer did not statistically differ from each other at a confidence level of 95%.

It is important to state the noticeable differences between the proposed and reference methods in terms of instrumentation, sample volume, cost per analysis and analysis time. In summary, the reference method is based on density measurements and the volume required for the determination of the alcohol content is about 100 mL. On the other hand, the foldable PADs are instrument-free and the amount of sample added on the PAD is 1 μL. Considering these features quite attractive, the cost per analysis on the proposed foldable PADs is about $ 0.01. In addition, the time required for the analysis of alcohol content is also another noticeable feature to be mentioned. While densitometric measurements are relatively fast, they require a previous distillation step, which is laborious and needs of temperature control. Oppositely, PADs offer the determination of alcohol content within 1 min at room temperature and without any previous sample pretreatment. In addition, wax-printed zones can also offer a rapid qualitative screening of the alcoholic content, as presented in the ESM (see Fig. S-2 and S-3).

3.5. Quantitative analysis of alcoholic content on foldable PADs

The alcohol content of whiskeys samples seized by Brazilian Federal Police was determined based on the analytical information extracted from the calibration curve previously presented in Fig. 4. The achieved values were compared with the expected alcoholic content as well as with the concentration found for the genuine sample of each brand. The obtained data are presented in Fig. 6. Prior to the screening of seized

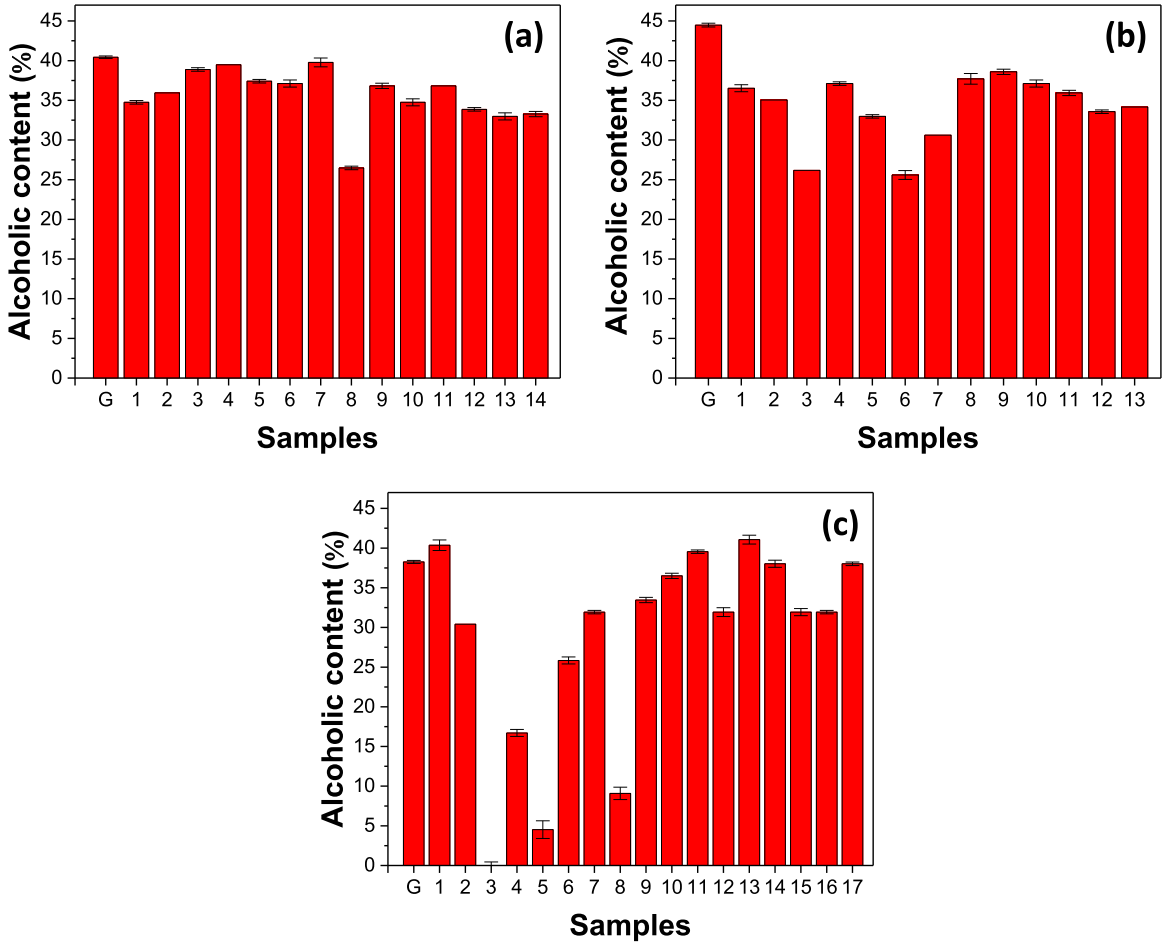

Fig. 6. Alcoholic content determined for seized samples from (a) RL, (b) BL and (c) NN brands using foldable paper-based analytical devices. The label G in all graphs mean the genuine sample analyzed under similar experimental conditions. For all data, the columns represent the average value while the error bar indicates the standard deviation for five measurements.

samples, genuine whiskey bottles from RL, NN and BL brands previously certified by the Federal Police were analyzed using the proposed approach. For each brand, a cut-off limit equal to three times the standard deviation below the average alcoholic content obtained for the genuine sample was defined for the sample classification, i.e., seized samples were classified as possibly adulterated when their concentrations were below this limit.

For the RL brand, the alcoholic content achieved for genuine samples was 40.4 ± 1.1% (n = 5). The authenticity of a total of fourteen seized samples was then checked. As can be seen in Fig. 6a, nine samples exhibited alcoholic content below the cut-off limit (37.1%). In this way, a total of ca. 64.3% of the seized samples for the RL brand was successfully classified as adulterated. Regarding the BL brand, an amount of thirteen seized samples were analyzed and, as denoted in Fig. 6b, twelve samples revealed alcoholic content below the cut-off limit (38.5%), thus allowing to state that ca. 92.3% of the analyzed samples were probably falsified. Finally, seventeen seized samples labeled as NN brand were analyzed on the foldable PADs similarly to others. Considering the alcoholic content in the genuine sample was equal to 38.2 ± 1.2% and the cut-off limit equal to 34.6%, a total of eleven seized samples (64.7%) presented concentration below this value, suggesting adulteration (Fig. 6c).

Overall, considering the cut-off limit of three times the SD below the average concentration for the genuine sample, the proposed foldable PADs enabled the classification of ca. 73% of the analyzed samples as being false whiskey. This strategy was quite reasonable and minimizes the possibility to obtain any incorrect identification. Additionally, the cut-off criteria include a safe range for forensic purposes allowing a preliminary screening with high feasibility to be implemented for using in the point-of-need.

4. Conclusions

This study has successfully described the development of foldable paper-based devices for performing redox titrations and determining the alcohol content in whiskey samples by visual detection. The proposed platforms offered good analytical performance and no statistical difference when compared to a reference method based on density measurements. The stability of the pre-spotted reagents has been limited to be ca. 40 min, which is enough to perform a complete titration. A linear behavior was achieved in a wide ethanol concentration range (0–50% m/v) with LOD equal to 2.1%.

Foldable PADs have also demonstrated great feasibility for forensic applications. The alcoholic content in a total of 44 whiskey samples from three different brands seized by the Brazilian Federal Police was analyzed and compared to genuine samples. Considering a cut-off limit equal to three times the standard deviation recorded for ethanol concentration in genuine samples, 73% of the seized samples were correctly classified as fake whiskeys.

Lastly, considering the low sample consumption (1 μL), the short analysis time (< 1 min), the portability (1 cm × 1 cm × 0.6 mm; width × height × thickness), the negligible cost per analysis (U$ 0.01) and the instrument-free platform, foldable PADs emerge as alternative prototypes for on-site forensic investigations. The use of foldable devices can still open new capabilities for on-site screening associating the multiplexed detection of illicit drugs and ethanol making possible the implementation of the proposed platforms for using at borders, police station, and/or transit monitoring.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.talanta.2018.10.036.

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