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Rapid screening of formaldehyde in food using paper-based titration

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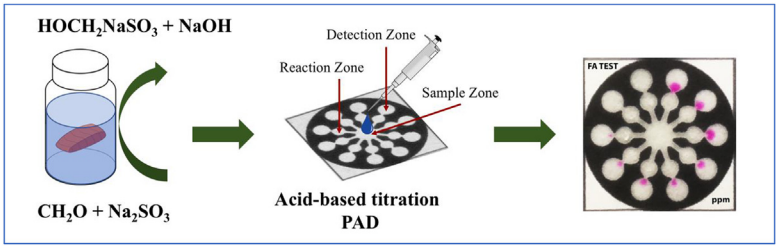
HIGHLIGHT

- PAD-based titration has been developed for simple and rapid screening of formaldehyde content in food.
- The number of color-change detection zones on the PAD are counted and equated to the formaldehyde concentration in the 100 mg L^{-1} intervals.
- The semi-quantitative can be done without any other detection instrument and the food color background occurred in the traditional test kits has been overcome.

GRAPHICAL ABSTRACT



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ABSTRACT

A simple paper-based analytical device (PAD) has been developed to rapidly detect formaldehyde (FA) in food samples. The analysis was based on sulfite assay where FA reacted with excess sulfite to generate sodium hydroxide (NaOH) that was quantified on PAD using acid-base titration. The PAD consisted of a central sample zone connected to ten reaction and detection zones. All detection zones were pre-deposited with polyethylene glycol (PEG) with phenolphthalein (Phph) as an indicator. Reaction zones contained different amounts of the titrant, potassium hydrogen phthalate (KHP). On flowing into reaction zones, the NaOH product reacts with KHP to reach the end point. In the presence of excess NaOH, unneutralized NaOH reached the detection zone and caused Phph color change from colorless to pink. In contrast, when NaOH was less than KHP, the detection zone remained colorless. Concentration of FA can be quantified from the number of pink detection zone(s) which were correlated with a known amount of pre-deposited KHP on the PAD. Total analytical process could be completed within 5 min. Areas of each zone and amounts of reagents added to the corresponding zones of the PAD were optimized to obtain reproducible and accurate results. PAD gave ranges of FA detection of 100–1000 mg L^{-1} with an interval of 100 mg L^{-1} and the limit of detection (LOD) was 100 mg L^{-1}. PADs were stable for up to a month under dark and cold conditions. Analysis of FA in food samples using PAD agreed well with those from the classical sulfite assay.

1. Introduction

Formaldehyde (FA) is considered as a carcinogen and classified as a Type 2 hazardous substance (Hazardous substance act, 1992.) [1]. It is used for many purposes such as animal preservation [2], equipment sterilization [3], textiles [4], furniture [5], cosmetic manufacture [6] and agriculture [7]. Recently, FA has been found in

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many foods from illegal use to maintain their freshness and prolong storage time [8,9]. FA intake is reported to cause neurological, respiratory and digestive problems [10,11]. Chronic and acute effects depend on many factors such as exposure time and physical fitness [12].

Several qualitative and quantitative analyses of FA in foods have been reported including gas chromatography (GC) [13,14], high performance liquid chromatography (HPLC) [15,16], spectrophotometric methods [17–19], enzymatic methods [20,21], and kinetic methods [22]. These methods provide effective analytical performance for low concentrations of FA but require relatively expensive and laboratory-based instruments and hence, may not suitable for on-site and rapid screening of FA. Consequently, colorimetric portable sensors have been developed for rapid, low cost and simple FA detection in food [23–26]. The quantitative or semi-quantitative colorimetric measurement of FA in food commonly relies on color intensity measurement using imaging software or portable smartphones or color comparison with a color reference card. However, accuracy of color intensity detection in food is problematic as a results of background interference from the food color. To eliminate food color interferences, sample preparations must be employed using various extraction methods that are time consuming, multistep process and relatively expensive making the sensors not suitable for rapid and cost-effective on-site analysis. An approach for FA analysis that can eliminate interference of food color background is the use of sulfite titration assay where the color change at the endpoint is observed instead of color intensity to quantify FA amount [27,28]. In this assay, FA in food reacts with excess sulfite to produce sodium hydroxide which is titrated with sulfuric acid using thymolphthalein as an indicator. A change of endpoint indicator color can be used to quantify FA in the samples. However, this classical titration requires much glassware, large volumes of titration solution, trained personnel, long analysis time and laboratory-based analysis.

An ideal sensor for FA detection in food would allow for the simple quantitative analysis without the need of sample preparation to eliminate food color interference and external color reference chart or color intensity measurement systems, provide for shorter analysis time and inexpensive on-site analysis. To accomplish this goal, we developed a paper-based analytical device (PAD) with the titration detection method to measure FA content in food samples. Since first introduced by the Whitesides group in 2007 [29], PADs have played an important role as an alternative analytical platform for environmental monitoring, medical diagnosis, and chemical screening [30,31]. PADs are low-cost, lightweight and hence portable, easy to construct and use and suitable for rapid analyses. PAD has been employed for FA detection using Hantzch reaction on paper to create fluorescent signal detected by a portable fluorescence detection system [32,33]. Although, these integrated systems could provide low level FA detection, they required a relatively complicated portable fluorescence detection box containing several components including a power supply, a cooling module, a detection box, a CMOS camera, two LED UV light source, a voltage controller, a chip holder, a hot plate, a connector and a smart phone. Recently, the Kaneta group introduced a titration-based detection system on PAD that requires no other external detection instruments. PAD-based titration systems have been used for acid-base titration and EDTA titration [34,35]. The principle of PAD-based titration is similar to that of classical titration but the end point is observed in the detection zone of the PAD instead of observing in the glassware in classical titration. Therefore, background sample color does not influence accuracy of the analysis since at the end point, the color change can still be observed through the use of a specific indicator. Moreover, glassware, trained personnel and large volume of sample and reagents were eliminated making on-site, rapid and ease of analysis possible using the PAD-based titration method.

In this study, PAD-based titrations were developed for quantitative analysis of FA in foods. The analysis is based on the sodium sulfite method where excess sodium sulfite reacts with FA in the sample to generate sodium hydroxide (NaOH) [27,28]. The NaOH product is quantified by dropping the NaOH on the PAD to perform an acid-base titration using sodium hydrogen phthalate (KHP) and phenolphthalein (Phph) as a titrant and an indicator, respectively (Fig. 1). On flowing into ten reaction zones, NaOH reacts with an appropriate amount of KHP that is deposited in different amounts on each reaction zone. In case of excess NaOH, the unneutralized NaOH reaches the detection zone and causes a color change from colorless to pink. When the amount of NaOH is less than that of KHP, the detection zone remains colorless. Concentration of FA can be interpreted from the number of color-changes in detection zone(s) which are equivalent to known amounts of pre-deposited KHP on the PAD. The initial PAD design was similar to that reported by the Kaneta group and used for acid-base titration [34]. However, since the amount of NaOH generated from the contaminated-level of FA in food analyzed by this work (100 mg L^{-1} or 3. 33 mM) is much lower than that reported previously (400 mg L^{-1} or 10 mM) [34], several modifications on the PAD have been carried out to obtain low-level analysis of NaOH product on PAD with accurate and reproducible results. The developed method was then tested for the stability as well as the accuracy with the standard sulfite titration method for FA analysis in food samples. The results showed similar FA contents in foods obtained from the two methods indicating that the developed sulfite assay with PAD-based titration method is effectively and successfully applied for rapid and on-site analysis of FA in food samples.

2. Experimental

2.1. Chemicals and materials

Formaldehyde IC standard (1000 mg L^{-1}) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetone (AR) and sulfuric acid (AR, 98%) were obtained from RCI Labscan Limited (Bangkok, Thailand). Phph, thymolphthalein, and bromothymol blue were obtained from Ajax Finechem (Australia) and cresol red was purchased from Fluka (Switzerland). D-glucose and polyethylene glycol (PEG) were purchased from Merck Millipore (MA, USA). Ethanol, sodium hydroxide, potassium hydrogen phthalate (KHP), and sodium sulfite were purchased from Loba Chemie (Maharashtra, India). All indicators were prepared by dilution of appropriate amount of indicator with 99% ethanol. Purified water prepared by Barnstead™ e-pure™ ultrapure water purification system was used throughout the experiments. Filter paper Grade 1 was purchased from Whatman (GE Healthcare Lifesciences, China) and a wax printer (ColorQube 8870) from Xerox (CT, USA).

2.2. Fabrication and preparation of the PADs

The PAD was designed using Adobe Illustrator CC 2017 containing a circular sample zone radially connected with ten reaction and detection zones, respectively. The design of the PAD was modified from Karita and Kaneta patterns [34] to facilitate detection of low concentrations of NaOH. Detail dimensions of each area of the PAD are in Fig. S1 (Supplementary Information). A wax printing technique was used to fabricate the PAD [36]. The designed PAD was printed onto a Whatman number 1 filter paper using a wax printer. The printed paper was then heated at 150 °C for 1 min on a hot plate. Clear adhesive tape was used to cover the backside of device to prevent leaking during analysis.

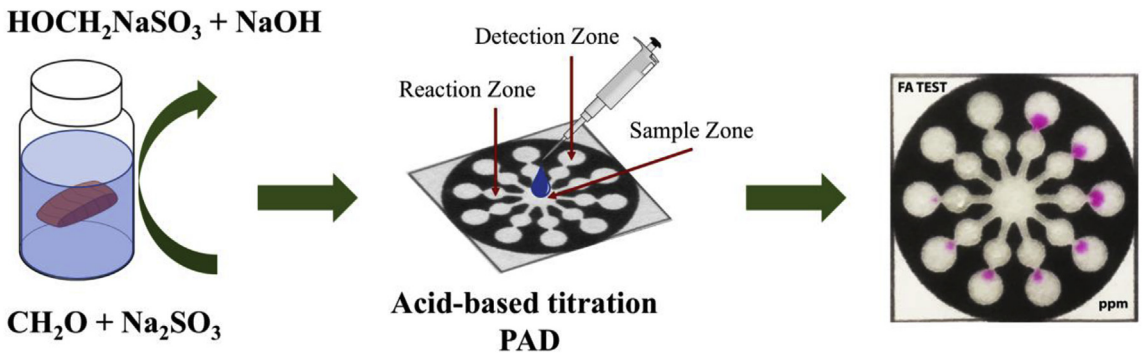

Fig. 1. Procedure for FA analysis in food samples using the paper-based titration method. The sample containing FA is mixed with sulfite solution in a vial to generate NaOH. The NaOH product is dropped onto the sample zone of the acid-base titration PAD to flow to 10 different reaction zones containing different amounts of KHP and then detection zones. The number of color-change detection zones containing pink spots indicates the concentration of FA in food samples in the 100 mg L^{-1} intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

For reagent storage, 1% w/v PEG (1.5 μL) and 1% Phph (1.5 μL) were stored in each detection zone. Each KHP concentration (0.75×2 μL) ranging from 0 to 29.9 mM with an interval of 3.33 mM to accommodate the detection of 100–1000 mg L^{-1} FA with an interval of 100 mg L^{-1} was deposited in each reaction zone (See Fig. S2, Supplementary Information). The device was allowed to dry between each reagent deposition.

2.3. FA analysis using PAD-based titration method

The analysis of FA using PAD-based titration were divided in two procedures, depending on sample preparation methods including laboratory-based preparation method as described in Section 2.5 and on-site method, where no need of sample preparation was required. For the analysis of FA in standard solution or in the sample prepared by the laboratory-based method, the FA containing solution (2 mL) was added to the pretreatment vial containing sodium sulfite (9 mg powder) to allow the reaction between sulfite and FA to generate NaOH occur. For on-site analysis, 2 g of the sample without any further sample preparation was added directly to the pretreatment vial containing sodium sulfite (9 mg) filled with 2 mL purified water and mixture allowed to react to generate NaOH. In both cases, after 1 min, the mixture containing NaOH products (30 μL) was added to the sample zone of the PAD. The color change at detection zones were observed after the solution completely filled all test zones. Number of pink detection zones were counted and interpreted as concentration of FA in the 100 mg L^{-1} intervals, for example, one pink detection zone is 100 mg L^{-1}, two pink detection zones is 200 mg L^{-1} and so on.

2.4. FA analysis using traditional sulfite titration method

Food samples were analyzed with PAD and the results validated against those obtained from the classical sulfite titration assay with the procedure following the ACS monograph and NIOSH analytical methods [27,28]. Briefly, the extracted sample solution (20 mL) was mixed with sodium sulfite solution (20 mL 0.1 M). After that, 3–5 drops of thymolphthalein was added as an indicator and the solution titrated with standardized sulfuric acid. The endpoint was measured when solution color changed from blue to colorless and FA concentration was calculated.

2.5. Sample preparation

Food samples including shrimp, squid, pickled squid, cow tripe, pickled ginger, and bamboo shoots were purchased from local markets in Chon Buri province, Thailand. Samples (50 g) were homogenized in a blender, mixed with 100 mL of purified water, sonicated for 20 min, centrifuged at 8,000 rpm (5 min) and filtered through Whatman#1 filter paper. The filtrate was stored at 6 °C until used. All sample filtrates were tested for acidity and basicity with pH strips, neutralized with either hydrochloric acid or sodium hydroxide and analyzed using the traditional sulfite titration method and the developed PAD-based titration method.

3. Results and discussion

3.1. Reagent selection for PAD-based titration

In this work, FA analysis is based on an acid-base titration of sulfite assay on the PAD. Classical sulfite assay can be performed by mixing FA with excess sulfite and the solution titrated with standardized sulfuric acid using thymolphthalein as an indicator [28]. Here, since the entire titration process was performed on the PAD, key reagents for acid-base titration have been modified from the classical sulfite assay and carefully selected. For standard acid titrant, sulfuric acid, known as a secondary standard, that burn and corrode the paper [37] was changed to a primary standard potassium hydrogen phthalate (KHP) [38] that is more compatible with the paper [34].

Suitable indicators for acid-base titration on PAD were also investigated including thymolphthalein and Phph. From 500 mg L^{-1} FA analysis (Fig. 2A), Phph produced an observable color change for all concentrations and treatments. The higher the Phph concentration the higher the color intensity. Thymolphthalein normally used in classical sulfite titration assay for FA detection, in contrast, produced no color change for all conditions tested on the PAD. Thymolphthalein has higher color transition pH from colorless to blue (9.3–10.5) than that of Phph (8.0–10.0, from colorless to pink) [39]. Therefore, Phph is more sensitive to the flowing NaOH to change the color from colorless to pink and was used for further experiments. From the analysis of 100 mg L^{-1} FA, only at the high concentration of 1% Phph with the polyethylene glycol (PEG) treatment gave the color change (Fig. 2B). Phph (1%) without PEG did not produce the color change on account of its low solubility in water making the detection zone hydrophobic. PEG was applied to the detection zone to improve zone hydrophilicity and wettability [40,41]. Therefore, NaOH can flow to the detection zones and react with the deposited Phph resulting in color change. Therefore, 1% Phph with PEG was used as a pretreatment reagent at the detection zones and applied for further experiments.

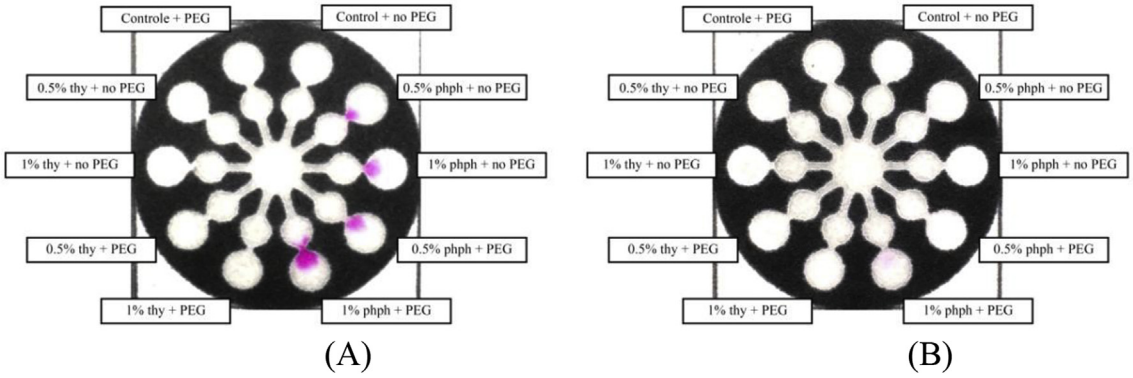

Fig. 2. Color of indicators for both phenolphthalein (phph) and thymolphthalein (thy) in different concentrations with and without polyethylene glycol (PEG) on a PAD. (A) 500 mg L^{-1} FA (B) 100 mg L^{-1} FA. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.2. Optimizations of the PAD design

The PAD used for FA analysis was fabricated for acid-base titration to quantify NaOH products from the FA and sulfite reaction. Initial dimension of the PAD was the same as the PAD-based titration developed by Karita et al. [34] that created the acid-base titration PAD with an acrylic plate holder to accelerate and direct the flow. Preliminary results from the analysis of 500 mg L^{-1} FA (16.67 mM) using this design showed a color change in all detection zones instead of the expected 5 color change detection zones (Fig. S3). Therefore, several modifications of the device design have been carried out to obtain accurate and precise analysis of FA and was discussed in Supplementary Information. These modifications included the removal of acrylic plate holder, changes of the device dimension such as increasing size of detection zones, decreasing the channel length that connected sample zone and reaction zones, and the treatment of hydrophobic area by PEG. Overall optimal conditions of PAD for FA analysis are summarized in Table S2 for reagent deposition at each zone, Fig. S1 for the device dimension and Fig. S2 for the deposition pattern of KHP at each reaction zones. Using the optimal condition, 5 color change detection zones were produced for 500 mg L^{-1} FA analysis as expected (Fig. 3). These optimal values were applied for further experiments.

3.3. Analytical features for standard FA analysis

Under optimal conditions, the performance of the paper-based devices was examined for analysis of FA in terms of detection range, reproducibility and limit of detection. The assay was first investigated for its ability to determine standard FA in the target concentration range,100–1000 mg L^{-1}, at intervals of 100 mg L^{-1}. Fig. 3 shows that semi-quantitative FA content can be equated to number of pink detection zones in the 100 mg L^{-1} FA intervals. For example, one pink-detection zone indicates 100 mg L^{-1} FA while 2 pink-detection zones indicate 200 mg L^{-1} FA and so on. Using this measurement, the user can simply count the pink detection zones to measure FA without any other detection instrument. Although, this system cannot provide detailed concentration of FA, it is suitably applicable for remote area as point-of-need measurement with rapid, cheap, and simple analysis is necessary. Moreover, unlike other FA test kits where the FA detection depends on color intensity and can be interfered by food color background, the developed PAD measured FA by observing number of color-change zones. Therefore, the problem of food color background normally found to interfere in other test kits was overcome using the developed method.

The limit of detection (LOD) was determined based on visual evaluation approach which is normally applied for non-instrumental methods by analysis of samples spiked with known FA concentration and by establishing the minimum level at which the FA can be reliably detected [42]. Here, the concentration was gradually reduced after adding 500 mg L^{-1} FA to the selected blank squid sample. The results showed that the lowest concentration that can be detected was 100 mg L^{-1} and hence, it was reported as LOD. Lower FA concentrations of 90 and 80 mg L^{-1} analyses did not give an observable pink color at the detection zones (Fig. S9, Supplementary Information). Although, the LOD obtained by our developed devices was higher than that obtained from the integrated platform containing PAD and a portable fluorescence detection system [32,33], it was below the FA level permitted to use in the USA which is 2.5 g/kg [43]. Moreover, good reproducibility from the analysis of standard FA with the concentrations in the detection range was obtained from the analysis of FA concentration in the detection range (Table S3, Supplementary Information).

3.4. Interferences

The effect of potential interferences in FA analysis was investigated using the compounds with similar functional group to the FA. Tested interferences included aldehyde compounds (acetaldehyde, butanal, salicylaldehyde and benzaldehyde), D-glucose and carbonyl compounds (acetone, 3-methyl-2-butanone, and acetophenone). Interferences and tolerance limit tests were performed using 500 mg L^{-1} of FA mixed with a given amount of interference. The method was considered to be interfered from the interference when color change at the detection zones were observed to be more or less than 5 zones. The proposed method has high tolerance to carbonyl compounds and low tolerance to short chain aldehyde compounds such as acetaldehyde since it is reactive to sulfite (Table 1) [44]. However, these compounds are naturally found in food at very low concentration (acetaldehyde: 18 mg L^{-1} [45]) and as an essential oil content which easily evaporates and has low solubility in water (butanal and salicylaldehyde) [46]. Therefore, we anticipated that these compounds will not interfere with this developed assay when applied for food analysis.

3.5. Analysis of FA in food

Performance of this paper-based titration assay was further evaluated for FA analysis in food samples that are often contaminated with FA such as seafood and vegetables [47,48]. Since FA analysis in the developed assay was based on the detection of generated NaOH using acid based titration on PAD, buffer capacity of the samples studied in this work was first evaluated for its effect

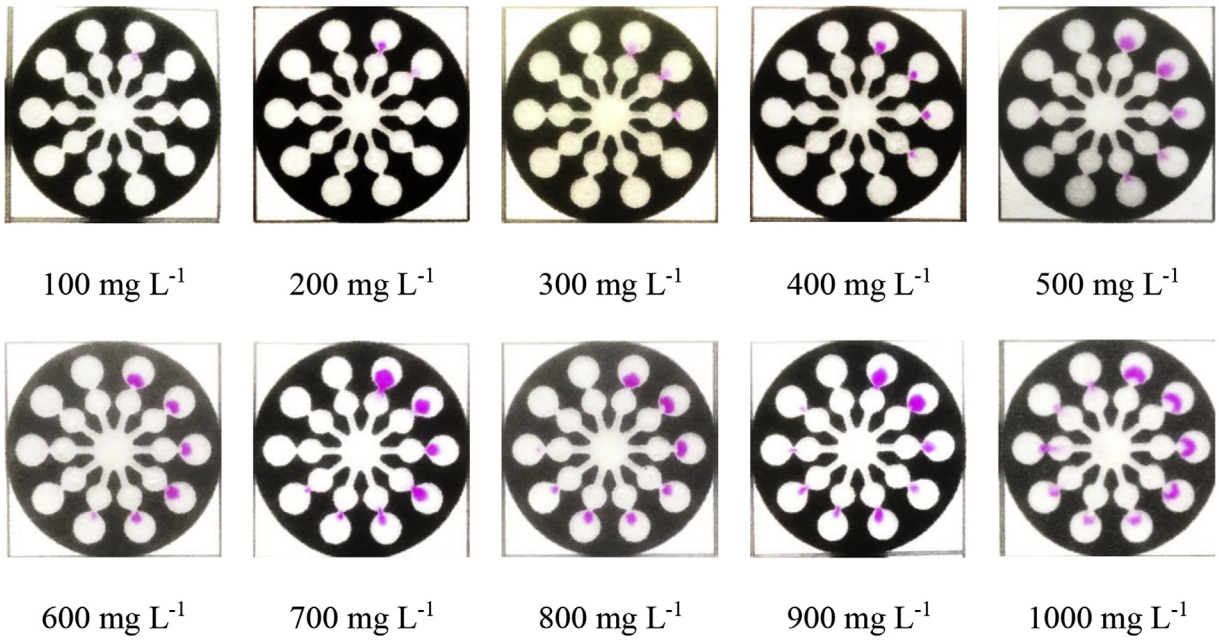

Fig. 3. Analysis of FA standard in the concentration range of 100–1000 mg L^{-1}.

Table 1
Tolerance limit of potential interferences for FA analysis using PAD-based titration.

Interferences	Tolerance Limit (mg L^{-1})
Acetaldehyde	80
Butanal	300
Salicylaldehyde	300
Benzaldehyde	>500
Acetone	>500
3-methyl-2-butanone	>500
Acetophenone	>500

on the analysis. As shown in the titration curve plotted of extracted sample pH with the added NaOH concentration (Fig. S10, Supplementary Information), all samples have low buffer capacity at pH 7 as demonstrated by the rapidly change of pH when small amount of NaOH was added. Prickled ginger has high buffer capacity at pH range of 4–5 but still low buffer capacity at pH 7. We anticipated that there was no effect from buffer capacity of the samples investigated in this work since all samples were neutralized prior to analysis as mentioned in experimental section. We next analyzed the samples using the developed method. Typical PAD from the analysis of FA in the different types of samples are demonstrated in Fig. 4 where the distinct color change at the detection zones were observed without any background interference from sample color. The obtained FA contents in the samples analyzed using the developed method were compared to those obtained from the classical sulfite titration methods to investigate the method accuracy. From Table 2, the results showed that FA content determined by the classical titration method were in the range of 34–862 mg L^{-1} and could not be detected in some samples. Using the developed method, the FA content in the samples were in the range of 100–800 mg L^{-1}. The sample containing FA concentration less than 100 mg L^{-1} could not be detected using the PAD since it is lower than LOD. However, for all 17 food samples, the two methods showed good agreement. These results indicated that the paper-based device is not only a suitable alternative for FA content analysis in food samples but is simpler, requires less sample and reagent and the analysis is faster to conduct than the classical sulfite titration assay. Moreover, the problem from color background interferences for FA analysis occurred in other test kits has been overcome using the developed assay.

The proposed assay was further investigated for its ability to use on-site by comparing the FA content obtained from the PAD analysis of the samples prepared by the laboratory-based extraction and the on-site sample preparation methods as described above. Samples of pickled ginger and cow tripe obtained from the PAD analysis using both sample preparation methods gave a similar range of FA concentrations (Table 3). However, laboratory-based sample preparation gave slightly higher FA concentration than on-site sample preparation from the analysis of crisp squid. These variations might be the results of the differences in sample texture. Pickled ginger and cow tripe are obtained as thinner and softer pieces than crisp squid and hence, there is more surface area per sample volume available for FA to react with sulfite and generate more NaOH. We expected that if the samples were cut as smaller pieces for on-site testing, the results of FA content would be similar to those obtained from the laboratory-based sample preparation method.

3.6. Stability study

The developed assay can eventually be applied for point-of-use and rapid detection of FA for on-site analysis. Thus, the PAD should have long storage time for conventional use. The stability of the paper-based device was evaluated over a period of time under the different storage conditions such as different light exposures (light and dark) and temperatures. All of the PADs were prepared on the same day and with the same reagents. The PADs were kept in clear plastic zipper bags. Devices for dark storage condition test were wrapped with aluminium foil. FA standard solution of 100 mg L^{-1} was freshly prepared for stability test. When stored at ambient temperature under light exposure, the PAD was stable only for 3 days. Thereafter, color changes of Phph at the detection zone were pale-and-unclear. When keeping in the dark, PAD can be kept longer up to 21 days after which color changes are pale-and-

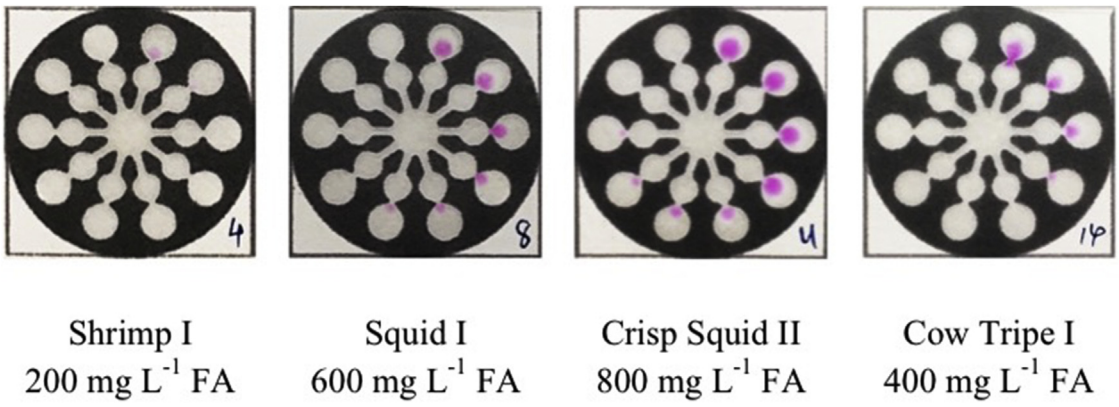

Fig. 4. Typical devices from the analysis of FA in real food samples.

Table 2
FA concentration in food samples obtained from classical titration method and the developed PAD-based titration method.

No.	Food Sample	Measured FA (mg L^{-1}) (n = 5)	
		Classical Titration	PAD-based Titration[a]
1	Pickled Ginger I	182.22 ± 0.56	100
2	Pickled Ginger II	81.48 ± 0.70	Undetectable
3	Pickled Ginger III	Undetectable	Undetectable
4	Shrimp I	271.50 ± 1.02	200
5	Shrimp II	154.44 ± 0.48	100
6	Shrimp III	51.36 ± 0.84	Undetectable
7	Shrimp IV	Undetectable	Undetectable
8	Squid I	689.16 ± 1.83	600
9	Squid II	34.86 ± 1.04	Undetectable
10	Crisp Squid I	458.22 ± 1.19	400
11	Crisp Squid II	862.20 ± 2.81	800
12	Crisp Squid III	Undetectable	Undetectable
13	Crisp Squid IV	48.84 ± 0.72	Undetectable
14	Cow Tripe I	434.36 ± 1.70	400
15	Cow Tripe II	93.87 ± 0.77	Undetectable
16	Bamboo Shoot I	Undetectable	Undetectable
17	Bamboo Shoot II	Undetectable	Undetectable

[a] Average concentration from five measurements.

Table 3
FA analysis in food samples using different methods of sample preparation and analyzed by the developed PAD-based titration.

Food Samples	FA concentration (mg L^{-1}) (n = 3)	
	Laboratory-based[a]	On-Site[a]
Pickled Ginger	100	100
Cow Tripe	400	400
Crisp Squid	700	600

[a] Average concentration from three measurements.

unclear. However, the PAD was stable for more than a month in the dark and cold (6 °C), likely attributable to Phph stability as indicated in the safety data sheet.

4. Conclusions

A rapid and simple paper-based titration assay was developed for semi-quantitative analysis of FA in food samples. The paper-based device was designed and optimized for accurate and reproducible results for acid-base titration to determine sodium hydroxide produced from the reaction of FA and sulfite. Under optimal condition, the FA can be detected in the range of 100–1000 mg L^{-1} with an interval of 100 mg L^{-1}. The limit of detection was 100 mg L^{-1} with high reproducibility obtained from the analysis of FA with the concentration in the detection range. The PAD titration assay also has high tolerance to the potential interferences normally found in food samples and was found to be stable for more than a month when stored at cold and dark conditions. The PAD assay was validated against classical sulfite titration method for the analysis of FA in food samples. Similar measured FA concentrations were obtained from both methods indicating a high degree of accuracy of the developed assay. Therefore, this new method is promising as an analytical tool for the rapid, low cost and point-of-use screening of FA in food samples.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2019.03.063.

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