Detection of vitamin C in various falsified oral formulations using voltammetry

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Abstract

Healthcare supplements are prime targets to be made into falsified products as they undergo less stringent regulation and can be purchased through online sites. There is an upsurge in the purchase of vitamin C due to the COVID19 pandemic which has made this product a target for falsification. Vitamin C can be available in various oral formulations and thus sample preparation is required prior to analysis. Chromatography and spectroscopy are the most widely used approaches for analysis. Therefore, this study focused on investigating if voltammetry could provide a rapid measurement approach of various formulations (normal, chewable, and effervescent tablets) of vitamin C without the need for any sample analysis. We found that tablet excipients reduce the oxidation peak current and influence the peak shape and oxidation peak potentials. This variation in the oxidation peak potential provided the ability to distinguish between the different oral formulations. Voltammetry provided the ability to conduct repeatable measurements and the solutions of the tablets were stable for 2 days for measurements. In a blinded study, voltammetry was able to identify the concentration of vitamin C present and the type of oral formulation of various falsified samples. Our findings highlight that voltammetry can be a vital technique for the determination of falsified healthcare supplements.

Keywords

Voltammetry, Vitamin C, chewable tablet, effervescent tablet, falsified medicines, formulations

1. Introduction

Falsified healthcare supplements are a major problem for society and can cause risk to public health, reduce confidence in healthcare systems, and cause economical loss [1-4]. Healthcare supplements already undergo less stringent regulation than pharmaceutical medicines and thus are prime targets to be made into falsified products by organised crime groups for financial benefit [5, 6]. Although many falsified products impact low- and middle-income countries, falsified healthcare supplements are prevalent in high-income countries, where they can be made accessible through online promotion. Internet security experts believe that nearly 25% of all e-mail, approximately 15 billion messages per day, are spam advertising counterfeit and/or unlicensed, unapproved drugs and healthcare supplements [7, 8].

Vitamin C also known as ascorbic acid is an essential dietary nutrient for a variety of biological functions [9, 10]. One of the core roles of vitamin C is to counteract inflammation and subsequent oxidative damage that play a major role in the initiation and progression of several chronic and acute diseases [11, 12]. Vitamin C is also implicated in aiding the immune system and is widely taken to reduce the impact of seasonal flu and colds [13]. Recently there has been an upsurge in the purchase of vitamin C during the COVID19 pandemic [14, 15], which has made this dietary nutrient a suitable target for falsification [16].

Vitamin C can be purchased in multiple oral dosage formulations. The most widely used are tablets, chewable tablets, and effervescent tablets. Therefore, there are various approaches for the determination of vitamin C in pharmaceutical preparations of which chromatographic approaches are the most widely used [17, 18]. Some of these methods require extensive sample preparation steps and thus are time-consuming and require specialist instrumentation which makes them less accessible to middle- and low-income

countries. An alternative approach has been to use electrochemical sensors, as vitamin C is easily oxidised [19, 20]. However, no studies have explored the potential for electrochemical detection as an approach for monitoring vitamin C in varying pharmaceutical formulations.

Within this study, we explored the potential of cyclic voltammetry as a suitable tool for rapid detection of vitamin C from various oral dosage forms. We explored the potential to conduct measurements in the presence of the excipients and thus reduce the requirements for sample preparation. We explored the impact of excipients from the different dosage forms on the accurate detection of vitamin C. The precision of the established method and the stability for routine robust monitoring were also explored. Finally, to assess if our established voltammetric method was capable of identifying falsified vitamin C tablets, we conducted a blinded trial to varied falsified compositions.

2. Materials and Methods

2.1. Tablets and chemicals

Vitamin C tablets, chewable tablets, and effervescent tablets (1000 mg dose) were purchased from Holland and Barrett. The composition of different formulations is shown in supplementary table 1. Ascorbic acid and potassium chloride were obtained from Sigma-Aldrich. Solutions of vitamin C tablet and ascorbic acid were prepared in a 1 M potassium chloride. The chemical utilised for the preparation of the falsified medicines is shown in Table 1.

2.2. Voltammetric determination of vitamin C

Electrochemical measurements were carried out with a CHI630B potentiostat, controlled with CH Instruments software (CH Instruments, Austin, TX, USA). A three-electrode system was used, where a 3mm glassy carbon electrode served as the working electrode, Ag|AgCl (3 M NaCl) electrode as the reference electrode, and a platinum wire as the counter electrode. Prior to electrochemical measurements, the glassy carbon electrode

was polished with alumina aqueous slurry. For all measurements, cyclic voltammetry was performed at 100 mV s^{-1} with a potential window of 0 to +1.2 V. To prepare the tablets for measurements, the tablet and chewable tablet were crushed to a coarse powder using a pestle and mortar and then was dissolved in 1 M KCl, whilst the effervescent tablet was directly placed into 1 M KCl. In all cases, the tablet solutions were then diluted to 40mg/ml for experimental studies. To compare the difference in the current response from tablets that were filtered, and unfiltered, various dosage forms were run in 40 mg/ml solutions. Half of these solutions were filtered using Grade 601 filter paper. Calibration responses were conducted using ascorbic acid powder and conducting serial dilutions of the various dosage forms. Calibrations were conducted in the concentration range of 4 to 40 mg/ml. For repeatability studies, 10 repeated cyclic voltammograms were carried out in 40 mg/ml solution of each formulation. Storage stability studies were conducted using 40 mg/ml solutions prepared from the tablet, chewable tablet, and effervescent tablet. These solutions were measured after days 1, 2, and 7.

2.3. Understanding the effect of excipients on the determination of ascorbic acid

Cyclic voltammetry measurements were carried out using a glassy carbon electrode at a scan rate of 0.1 Vs^{-1} between a potential range of 0 – 1.2 V to determine if the excipients influenced the oxidation of ascorbic acid. Voltammetric responses were obtained for solutions of 100 mg/ml of sorbitol (sweetener), silicon dioxide (anti-caking agent), and microcrystalline cellulose (bulking agent) in the presence and absence of 40 mg/ml ascorbic acid. Cyclic voltammograms of the excipients within the same potential window were also conducted to explore if they were also oxidisable.

2.4. Determination of falsified vitamin C

Table 1 shows the different falsified tablets that were produced and tested using voltammetry. Most falsified products reduce or remove the amount of the active ingredient through using more bulking agents or utilise cheaper excipients. We aimed to make formulations which would mimic these factors [21]. All falsified tablets were made using

the original tablets which were grinded down and mixed with the additional components shown in Table 1. The aim was to make formulations which were made to similar weight/appearance, where alternative active compounds used had similar molecular weights. Excipients were used to tailor the compositions so that the falsified tablets could resemble the three different formulations. The falsified tablets were made as powders and thus did not require to be crushed prior to conducting cyclic voltammetry measurements. The researcher conducting the electrochemistry measurements were blinded to the composition of the falsified samples.

Table 1. Composition of the chemical components that were made to falsified normal, chewable or effervescent tablets.

Sample number	**Content of ascorbic acid (mg)**	**Other excipients present**
1	324	1200mg lactose
2	0	1000mg D-sorbitol and 700mg lactose
3	0	1000 mg citric Acid and 700 mg lactose
4	500	1322.5mg of lactose
5	700	793.5mg of Maize Starch
6	500	1000mg of citric acid and 1000mg sodium bicarbonate
7	250	3000mg sucrose
8	1000	1500mg citric acid and 1500mg sodium bicarbonate
9	0	1000mg orange flavour powder, 1000mg sucrose, 500mg of citric acid and 500mg sodium bicarbonate

2.6. Data analysis

For all measurements, the data was plotted to show the mean ± standard deviation. Statistical analysis was carried out using GraphPad Prism, where data was compared using one-way or two-way ANOVA.

3. Results and Discussion

3.1. Measurement of vitamin C in the presence of excipients

Minimal sample preparation can provide accurate detection and can also reduce the total analysis time. Therefore, we explored the ability to conduct the measurement of three different formulations filtered or unfiltered. Figure 1 shows cyclic voltammetric responses of the normal, chewable, and effervescent tablet where no difference was observed in the response between the filtered and unfiltered response. Figure 1D shows the overall responses, where there was no significant difference between the samples of the tablet which were filtered and unfiltered (n=4). These results indicate that measurement of vitamin C can be conducted in the presence of the excipients and thus reduce the need for extra sample preparation steps in the measurement of oral formulations.

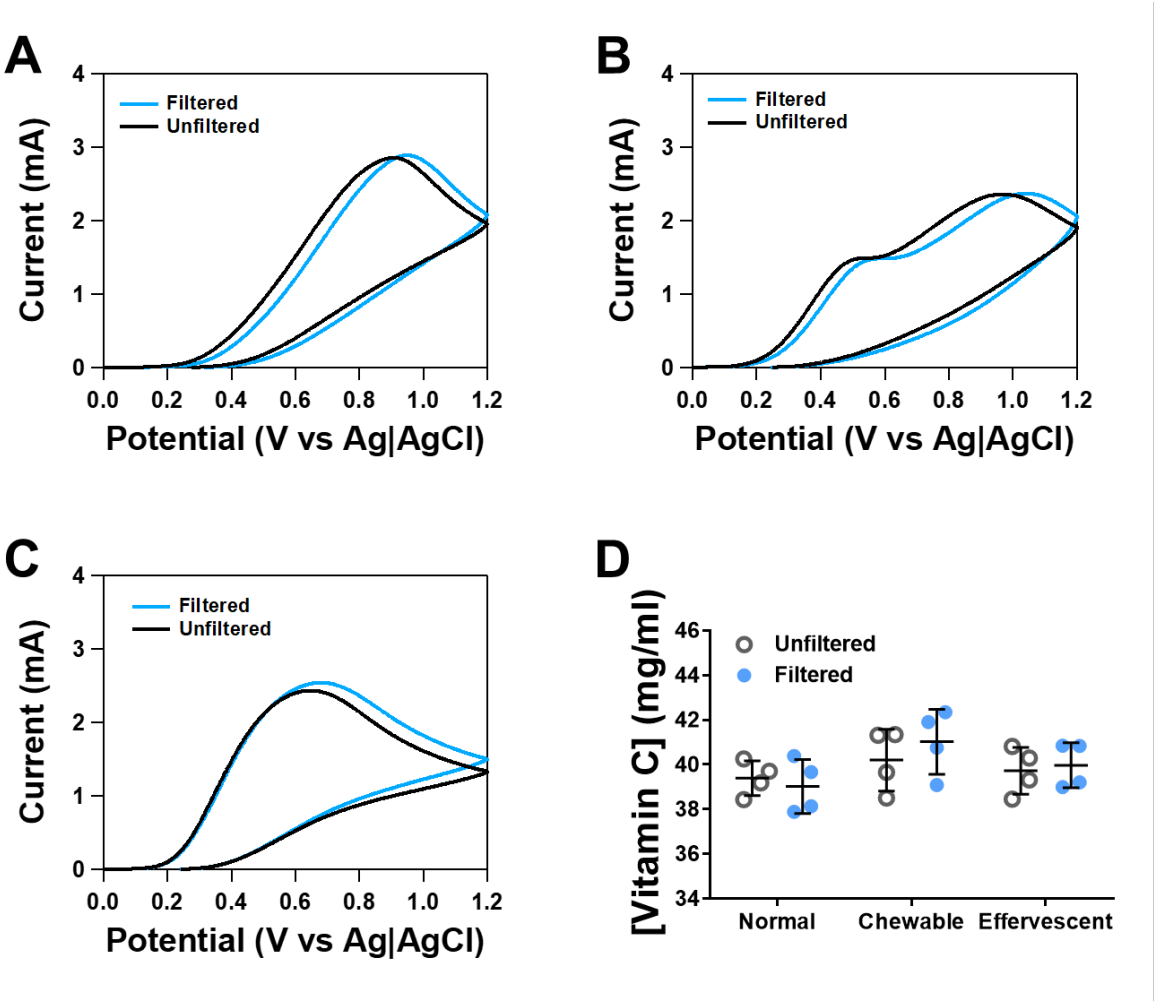

Figure 1. Measurement of vitamin C tablet in the presence of excipients. Voltammetric responses from (A) normal tablet, (B) chewable tablet and (C) effervescent tablet. (D) Comparison of the concentration of vitamin C observed when comparing tablet where voltammetric measurements were conducted in the presence and absence of excipients. Data shown as mean ± S.D., n=4.

3.2. Calibration of vitamin C using voltammetry

Calibration responses were first carried out using an ascorbic acid standard to compare to the calibration responses of the 3 different oral dosage forms. Supplementary figure 1 shows cyclic voltammograms of ascorbic acid and the resultant calibration obtained from repeated measurements. The oxidation peak potential was observed at 0.85 V for the

40mg/ml ascorbic acid standard. From the calibration plot shown in supplementary figure 1, the sensitivity was 92 ± 1 μA mg/ml^{-1} and the limit of detection was 2 mg/ml (n=4). The calibration response for ascorbic acid was compared to that of the 3 oral dosage forms.

For the normal tablet, the voltammograms are shown in Figure 2A, where the oxidation was 0.92 V, which was slightly more positive than that of the ascorbic acid standard. The calibration response for the normal tablet is shown in Figure 2D, where the sensitivity was 69 ± 1 μA mg/ml^{-1} and the limit of detection was 4 mg/ml (n=4). There was a significant reduction in the sensitivity of the calibration response when compared to ascorbic acid ($p<0.001$). The voltammograms for the chewable tablet are shown in Figure 2B, where two oxidation peaks were observed. The first oxidation peak was at 0.54 V and the second peak was 1.0 V. Given that ascorbic acid has one oxidation peak potential, the early peak potential may be due to oxidation of an excipient present within the chewable tablet. The second oxidation peak was utilised to generate the calibration response shown in Figure 2E. The sensitivity was 59 ± 1 μA mg/ml^{-1} and the limit of detection was 5 mg/ml (n=4). This response was lightly lower than that on the normal and effervescent table most likely due to the first oxidation peak impacting the analysis of the second oxidation peak. There was a significant reduction in the sensitivity of the calibration response when compared to ascorbic acid ($p<0.001$, Figure 2E). Cyclic voltammograms for different concentrations of the effervescent tablet are shown in Figure 2C, where the oxidation peak potential was 0.65 V and significantly lower than that of the ascorbic acid standard. The sensitivity was 67 ± 1 μA mg/ml^{-1} and the limit of detection was 7 mg/ml (n=4, Figure 2F). There was a significant reduction in the sensitivity of the calibration response when compared to ascorbic acid ($p<0.001$).

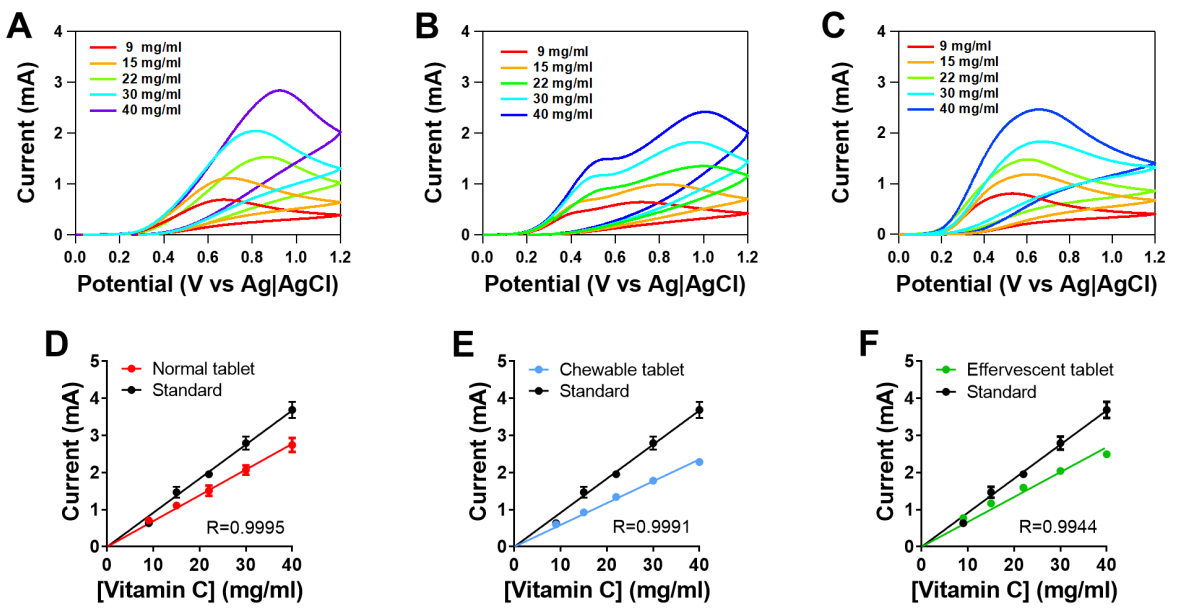

Figure 2. Calibration responses obtained from tablet using serial dilution. Voltammetric responses from (A) normal, (B) chewable and (C) effervescent tablet. Calibration responses were compared to the calibration of standard ascorbic acid, where responses are shown for (D) normal, (E) chewable and (F) effervescent tablet. In each case the response from the table was significantly lower than that of the ascorbic acid standard. Data shown as mean ± S.D., n=4.

For all the formulations, there was an oxidation peak potential that was different from that of the ascorbic acid standard, suggestive that the oxidation of ascorbic acid in the vitamin C formulations is being affected by the presence of the excipients. The differences in oxidation peak and shape of the voltammogram for the three different oral formulations can be of significant benefit as it can provide the ability to distinguish between the different formulations. The effect of the excipients also reduced the oxidation peak current observed in the three formulations when compared to the ascorbic acid standard. These results indicate that the excipients present influence the determination of ascorbic acid and similar observations have been observed when voltammetry has been used to measure other pharmaceutical and healthcare products [22, 23].

3.2. Effect of excipients on the voltammetric determination of ascorbic acid

Our findings showed that the oxidation peak potential and current of ascorbic acid present within the tablet was much lower than the standard, suggestive that the presence of the excipients influenced the measurement. Therefore, we explored the presence of common excipients present within the different formulations which have been shown previously to influence the voltammetric measurement [22]. One of the key differences that occurred due to the presence of the excipients within the effervescent tablet was the pH of the solution became more alkaline due to the presence of sodium hydrogen carbonate. Figure 3 shows the effect of individual excipients on the oxidation peak potential and current response. In all cases, the excipient alone did not have a faradaic response however when mixed with ascorbic acid resulted in a clear reduction of the peak potential.

Figure 3A shows that the presence of microcrystalline cellulose (MCC), which is used as a binder in a normal tablet, reduced the oxidation peak current significantly of ascorbic acid by half ($p<0.001$, $n=3$, Figure 3D) when compared to the current of ascorbic acid alone. There was no difference in the oxidation peak potential. Figure 3B shows the influence of silicon dioxide on the voltammetric response of ascorbic acid. Silicon dioxide acts as a glidant and was present in both the normal and chewable tablets. The oxidation peak current of ascorbic acid when silicon dioxide was present was half when compared to the ascorbic acid response alone ($p<0.001$, $n=3$, Figure 3D). When measurements were carried out in silicon dioxide, the oxidation peak potential was 100 mV greater than that of ascorbic acid alone. This increase in oxidation peak potential was observed in both the normal and chewable tablets and thus could be because of silicon dioxide. In Figure 3C, the response of sorbitol on the voltammetric response of ascorbic acid is shown. Sorbitol is present in the chewable and effervescent tablet as a sweetener. There was a significant reduction in the ascorbic acid response in the presence of sorbitol when compared to when it was absent ($p<0.001$, $n=3$, Figure 3D). Sorbitol however reduced the oxidation peak potential of ascorbic acid by ~50 mV. This excipient alongside the presence of sodium hydrogen carbonate might explain the reduction in the oxidation peak potential observed in the effervescent tablet when compared to the ascorbic acid

standard. For the chewable tablet there are two oxidation peaks, which may be due to ascorbic acid being oxidised at varied voltages due to the influence of excipients, as this tablet contains excipients that both increase and reduce the oxidation peak potential.

Our results have shown that the presence of excipients can have a significant influence on the oxidation peak current and voltage and thus for accurate determination of the concentration, calibration responses need to be conducted in the presence of excipients. We have previously shown that the concentration of excipients does not significantly affect the current observed [22]. The amounts different excipients added by suppliers is fixed due to tablet size and our calibrations from the normal and effervescent tablet are identical even though the composition is signficant varied. Calibrations in real tablets are essential as standards to validate and compare products with any suspected falsified product. The influence of excipients on the oxidation peak potential also provides the ability to clearly identify the presence of different formulations of the same active ingredient.

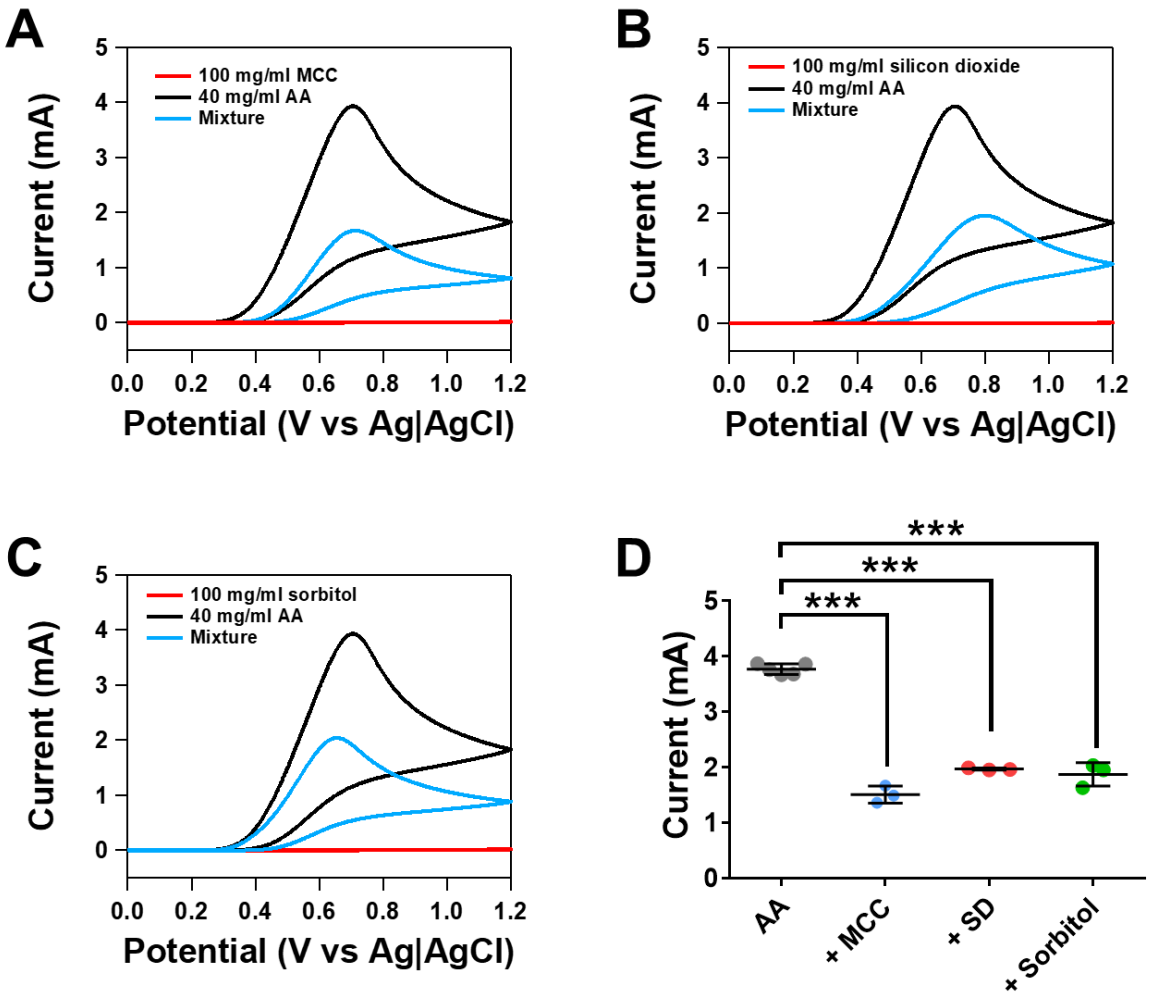

Figure 3. The effect of individual excipients on the oxidation peak current and potential of 40 mg/ml ascorbic acid. (A) Shows the effect of 100 mg/ml microcrystalline cellulose (MCC) on ascorbic acid, (B) shows the effect of 100 mg/ml silicon dioxide on ascorbic acid and (C) shows the effect of 100 mg/ml sorbitol on ascorbic acid. (D) shows the difference in the oxidation peak current of ascorbic acid (AA) in the presence of microcrystalline cellulose (+MCC), silicon dioxide (+SD) and sorbitol. Data shown as mean ± S.D., n=5-3, ***p<0.001.

3.3. Repeatability and storage stability studies

Repeatability studies in each different formulation were carried out to evaluate the precision of the voltammetric method. Figure 4 shows 10 repeated measurements in a single tablet for the 3 different formulations, where no significant difference was observed

between the ten measurements indicating that the voltammetric method could conduct reproducible measurement of individual tablets.

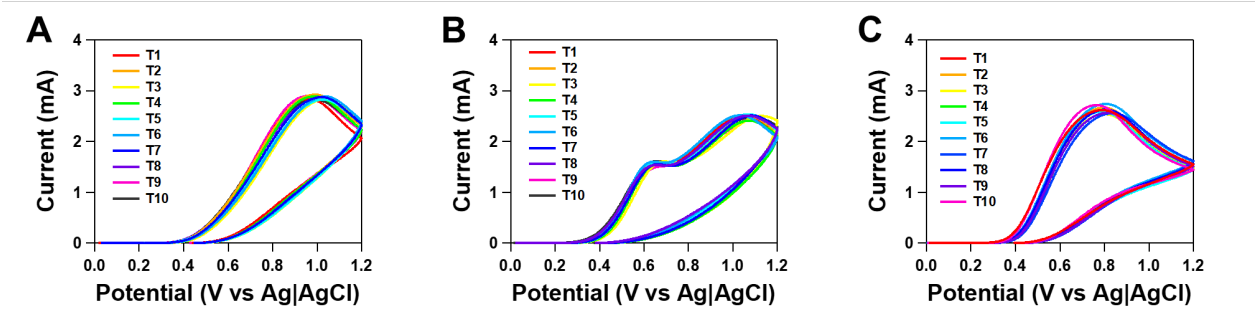

Figure 4. Reproducibility studies. Voltammograms showing ten measurements of (A) normal (B) chewable and (C) effervescent tablet.

After the tablet was crushed into a coarse powder and dissolved in 1 M KCl, the duration that the sample could be stored prior analysis and still provide an accurate measurement was investigated further as it may not be possible when conducting measurement of falsified medicines to do so directly at the point of source. Therefore Figure 5 shows the initial voltammogram of 3 different formulations and then the responses observed after 1, 2, and 7 days. There was no noticeable difference in the voltammogram of the normal tablet from the initial response from that observed in 7 days (Figure 5A). There was minimal difference in the voltammogram from initial to the first 2 days in both the chewable and effervescent tablets, but then the voltammogram had an altered shape and reduced response after day 7 (Figure 5B & C).

There was no significant difference in the amount of vitamin C observed in the normal tablet from the initial response to after measurement of the same solution on day 7 (n=3, Figure 5D). There was a significant reduction in the current of the chewable tablet on day 7 when compared to initial ($p<0.001$), day 1 ($p<0.001$), and day 2 response ($p<0.01$, n=3). There was a significant reduction in the current of the effervescent tablet on day 7 when compared to initial ($p<0.01$), day 1 ($p<0.01$), and day 2 response ($p<0.05$, n=3). For measurement of the chewable and effervescent tablet, the solution is stable for 2-day

post preparation for measurement, whilst this is extended to 7 days for the normal tablet. Solid vitamin C is very stable, however, when dissolved in water, it decomposes and is influenced by factors such the presence of trace metals [24]. For the effervescent tablet, zinc is present which may explain the rate of decomposition. However, none of these excipients were present within the chewable tablet, which was also decomposed over time. Another study has shown that the stability of ascorbic acid can be affected in sorbitol solutions [25], which is present in both chewable and effervescent solutions. Therefore, this highlights those solutions of the 3 different tablet formulations that can be stored prior to analysis for determination of falsified detection and thus provides increased scope for measurement in low- and middle- income countries.

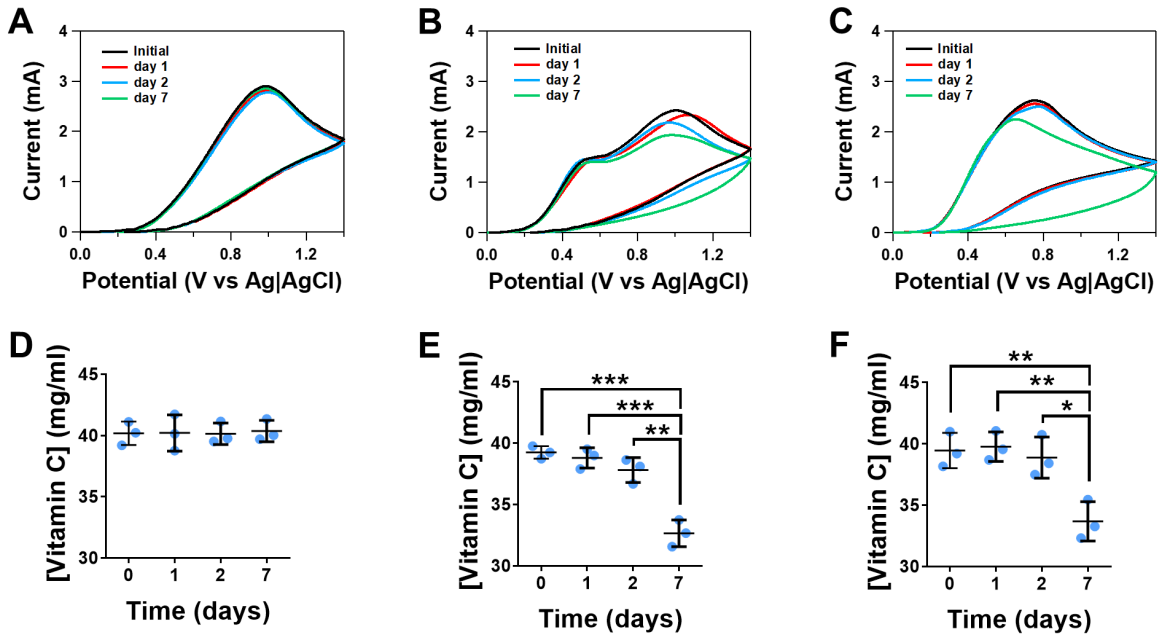

Figure 5. Storage stability of tablet solutions. Voltammograms showing initial response of prepared solutions of (A) normal (B) chewable and (C) effervescent tablets and after storage for day 1, 2 and 7. Measured concentration of vitamin C from prepared solutions of (A) normal (B) chewable and (C) effervescent tablets over the duration of 7 days. Data shown as mean ± S.D., n=3, *p<0.05, **p<0.01 and ***p<0.001.

3.4. Studies using falsified vitamin C preparations

To access the suitability of our established method using voltammetry for the measurement of falsified medicines, blinded samples were prepared and run using the established method. Supplementary figure 2 shows the powdered samples that were provided and the resultant voltammogram responses obtained for the nine different samples in comparison to the 40 mg/ml vitamin C solution obtained from the normal, chewable, and effervescent tablet. From the powdered samples provided, samples 6 and 7 appeared yellow in colour and sample 9 was off-white, whilst all other samples were white in appearance. Both the normal and chewable tablet appeared white/off-white as a crushed powder, whilst the effervescent tablet was slightly yellow in appearance and thus indicative that falsified samples 6 and 7 may be effervescent tablets.

Sample 1 had an oxidation peak potential that matched that observed for a normal tablet. This sample contained 325.1 ± 3.1 mg of vitamin C and thus this was matched to the amount present as shown in table 1. Sample 2 and 3 had no observable response and therefore indicates that no vitamin C was present. Additionally, the excipients used to make samples 2 and 3 did not generate a false positive faradaic peak. Sample 4 contained two oxidation peaks and thus most likely was a falsified chewable tablet. The sample contained 499.6 ± 4.2 mg of vitamin C and thus this was matched to the amount present as shown in table 1. In a similar fashion, sample 5 also resembled a chewable tablet due to the presence of two oxidation peaks. The sample contained 699.2 ± 6.2 mg of vitamin C and thus this was matched to the amount present as shown in table 1. Sample 6 had an oxidation potential peak that did not match that of any formulation but was closest in shape and oxidation peak potential to that of an effervescent tablet. The sample contained 500.3 ± 5.7 mg of vitamin C and thus this was matched to the amount present as shown in table 1. Sample 7 also had an oxidation peak potential that was closest to the effervescent tablet and thus was assumed to this formulation. The sample contained 253.4 ± 7.3 mg of vitamin C and thus this was matched to the amount present as shown in table 1. Sample 8 had an oxidation peak potential that matched that of the normal tablet. On analysis, we observed that the sample contained 1001.7 ± 4.4 mg of vitamin C and thus this was matched to the amount present as shown in table 1. This also

indicated that sample 8 was not altered in terms of the dosage of vitamin, but only by the presence of alternative maybe cheaper excipients. Finally, sample 9 contained no evident faradaic response and thus most likely did not contain any ascorbic acid.

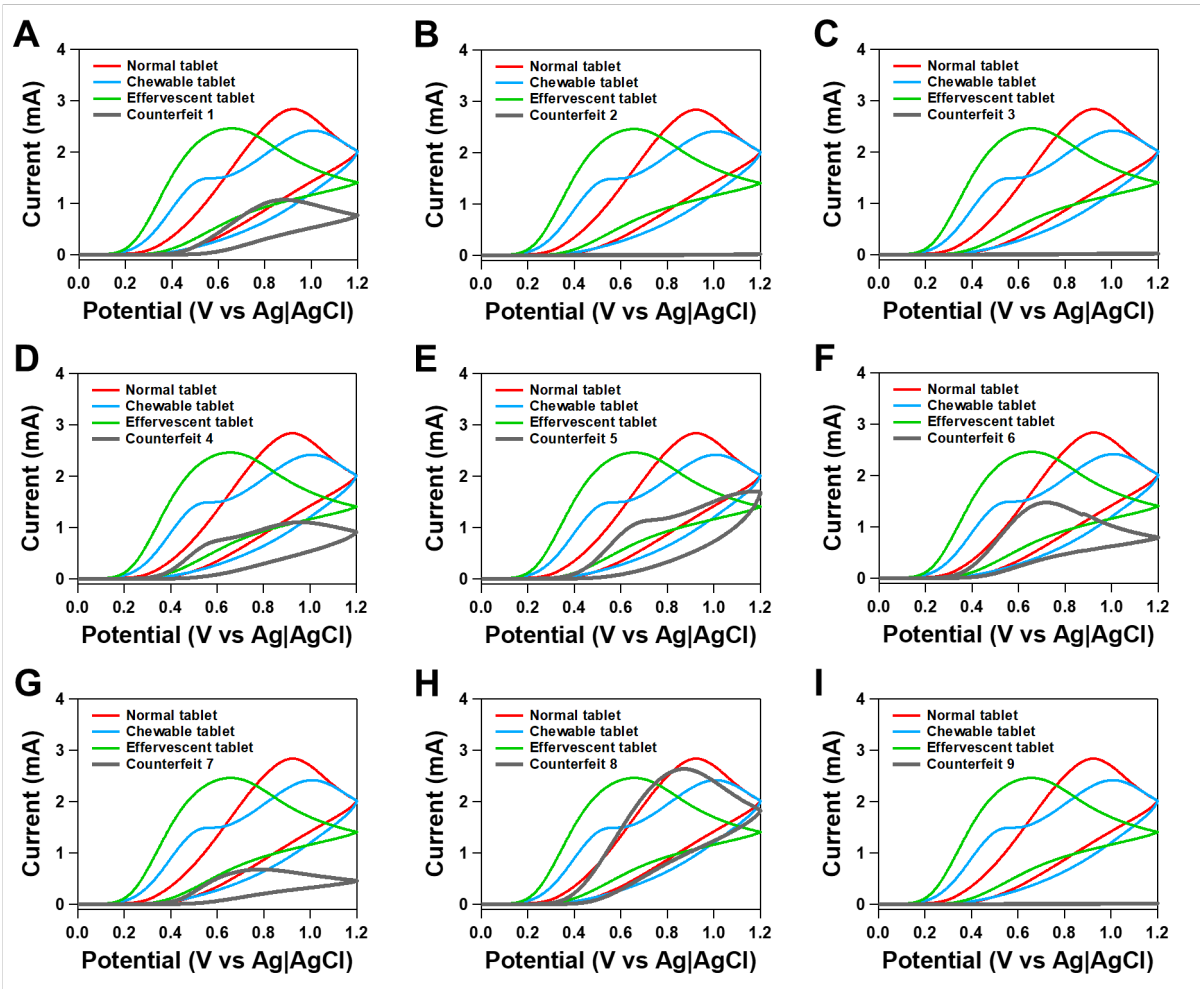

Figure 6. Voltammograms of different falsified samples with comparison to that of 40 mg/ml vitamin C from a normal, chewable, and effervescent tablet.

Overall voltammetry provided the ability to clearly identify the varying samples of falsified samples where an accurate determination of the presence of lower concentration of vitamin C was achieved irrespective of the type of oral formulation that was falsified. However, like any analytical approach, voltammetry has limitations, where substances

that can be oxidised at the same voltage as vitamin C can cause interference and falsely indicate that the active ingredient might be present within the tablet.

4. Conclusion

Vitamin C is an important health supplement that plays a variety of biological roles. Falsified vitamin C has been made accessible through online promotion to consumers and thus rapid approaches for the detection of falsified products are needed. Most approaches for the determination of vitamin C are based on using chromatographic and spectroscopic methods, which require extensive sample preparation and thus are time-consuming. When measurements were carried out in the presence of the excipients, the current response was reduced, the peak shape and oxidation peak potential was altered, which provided the ability to determine different vitamin C oral formulations. Voltammetry provided the ability to detect different falsified oral formulations without the requirement of extensive sample preparation. Our findings highlight that voltammetry can be a simple and robust approach for the determination of falsified health supplements.

CRediT authorship contribution statement

Chloe Miller: Methodology, Investigation, Validation, Formal Analysis, Writing – Original Draft; ***Petra Kristova:*** Methodology, Resources, Writing – Review & Editing; ***Bhavik Patel:*** Conceptualization, Methodology, Resources, Formal Analysis, Writing – Review & Editing, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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