3D printed electrochemical pestle and mortar for identification of falsified pharmaceutical tablets

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Abstract

Falsified medicines and healthcare supplements provide a major risk to public health and thus early identification is critical. Although a host of analytical approaches have been used to date, they are limited, as they require extensive sample preparation, are semi-quantitative and/or are inaccessible to low- and middle-income countries. Therefore, for the first time we report a simple total analysis system which can rapidly and accurately detect falsified medicines and healthcare supplements. We fabricated a poly-lactic acid (PLA) pestle and mortar and using a commercial 3D printer, then made carbon black/PLA (CB/PLA) electrodes in the base of the mortar using a 3D printing pen to make an electrochemical cell. The pestle and mortar were able to crush and grind the tablets into a fine powder to the same consistency as a standard laboratory pestle and mortar. Using

melatonin tablets to characterise the device, the 3D printed pestle and mortar was able to detect the concentration of melatonin in the presence of insoluble excipients. The calibration plot showed a linear response from 37.5 to 300 µg/mL, where the limit of detection was 7 µg/mL. Electrochemical treatment was able to regenerate the CB/PLA working electrode allowing for repeated use of the device. In a blinded study, the device was able to accurately determine falsified melatonin tablets with recovery percentages between 101 and 105 %. This was comparable to HPLC. Overall, these findings highlight that our 3D printed electrochemical pestle and mortar is an accessible and effective total analysis system that can have the ability to identify falsified medicines and healthcare supplements in remote locations.

Keywords

3D printed electrodes, carbon black, pestle and mortar, pharmaceutical analysis, falsified medicines, melatonin, vitamin C

Introduction

Falsified medicines and 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]. Most falsified medicines are made using poor manufacturing and limited to no quality control practices [2, 5, 6]. The impact of falsified medicines is mainly felt in low- and middle-income countries where accessibility to medicines is often poor. 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 [7, 8]. 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-mails, approximately 15 billion messages per day, are spam advertising counterfeit and/or unlicensed, unapproved drugs and healthcare supplements [9, 10].

The majority of falsified medicines and healthcare supplements contain little or no active pharmaceutical ingredient (API) [11, 12]. Given that analytical techniques need to accurately monitor concentration and identity the presence of APIs, this makes it difficult for a uniform detection approach. The most widely used analytical techniques for determination of falsified medicines and healthcare supplements are based on pharmacopoeia assays. Techniques such as high-performance liquid chromatography (HPLC) with ultraviolet spectroscopy (UV) and/or mass spectrometry detection or gas chromatography [13-15] are widely used. These methods can provide high sensitivity and selectivity but require highly technical expensive instruments and expertise. Therefore, these robust approaches are not easily accessible for low- to middle-income countries,

where the greatest need for analytical detection is required [16]. Rapid and simple approaches which can also be used in remote locations such as colorimetry and thin-layer chromatography (TLC) [17-19] are usually less sensitive and require extensive sample preparation but require less expertise. Spectroscopic methods such as near-infrared, mid-infrared (MIR), Raman and benchtop nuclear magnetic resonance [20-23] provide the ability to identify the API rather than provide accurate analysis of concentration. These techniques are costly and require high level of expertise. Most current techniques and methodologies require significant sample preparation time to extract the API for analysis.

3D printing has revolutionised the ability to creatively manufacture analytical devices that can be used for multiple functions from reaction-ware, flow cells and electrochemical devices [24-29]. Being able to interface electrochemical sensors into varying devices has provided the ability to generate total analysis systems, where sample preparation, manipulation and analysis can all be conducted within one simple device. Additionally, 3D printed devices are sustainable due to the use of biodegradable polymers, such as polylactic acid (PLA) and provide the ability to manufacture globally with cheap production costs. This approach to manufacturing makes 3D printing highly attractive for making a new generation of analytical devices. Electrochemical cells have already been produced in a single step with 3D printed electrodes embedded within thermoplastic wells and have been shown to monitor a host of important chemical analytes [30, 31]. A previous study has shown the potential for 3D printed electrochemical wells for the screening of pharmaceutical drugs [32]. However, to date there are no total

analysis systems for measurement of the concentration of an API in a medicine or healthcare supplement in a single step.

Within this paper, we developed a 3D printed electrochemical pestle and mortar device to conduct total analysis of a pharmaceutical tablet. Melatonin tablets, which have been subject to being falsified [33-35], were chosen as an exemplar to showcase the potential of the device. Carbon black/poly lactic acid (CB/PLA) electrodes were embedded into a 3D printed PLA mortar. The performance of the 3D printed pestle and mortar was evaluated to observe if this could crush and grind the tablet into a fine powder. The electrochemical analysis of the 3D printed mortar was carried out using melatonin tablets and the scope of the device was highlighted using a variety of other pharmaceutical tablets. Lastly, in a blinded study, we evaluated the ability of our device to determine a range of prepared falsified melatonin formulations.

Experimental Section

Fabrication of the 3D printed electrochemical pestle and mortar

The 3D printed pestle and electrochemical mortar mould were printed using PLA on a Raise 3D Pro (Irvine, USA) printer. The schematics of the electrochemical mortar mould are shown in **Figure 1A & B**, where circles are extruded cut into the base of the mortar to place the electrodes to make an electrochemical cell. The electrical connection was also achieved through the base of the mortar. The working and reference electrodes were 5 mm in diameter and the counter electrode was 6 mm in diameter. Prior to making

the electrodes, silver wire was fed through the back of the mortar and coiled to sit in the base of the mould where the electrodes were to be placed. This would form the electric contact to the electrodes.

To fabricate the electrodes, the extruded cut circle moulds within the mortar were all filled with CB/PLA (marketed as proto pasta, was purchased from filaprint, UK) using a 3D printing pen (SUNLU 300) with a 0.75 mm nozzle and printing speed of 3600 mm/s. When filling the mould, the CB/PLA was compressed whilst in the semi-molten state by mechanical pressure using a metal rod. To ensure the surface area of the electrode was uniform, the electrodes were mechanically polished using 1200 grit abrasive paper. Following this the surface electrodes were polished in a 0.3 μm alumina suspension for 3 minutes. The reference electrode was then finely painted using silver conductive paint (Electrolube, UK). A photograph of the final pestle and mortar can be seen in **Figure 1C**. Prior to conducting studies, electrochemical pre-treatment was performed in 0.5 M NaOH by holding the potential at +1.4 V for 200 s and then at -1.0 V for 200 s which has previously been shown to be an effective approach for the activation of CB/PLA electrodes [36, 37].

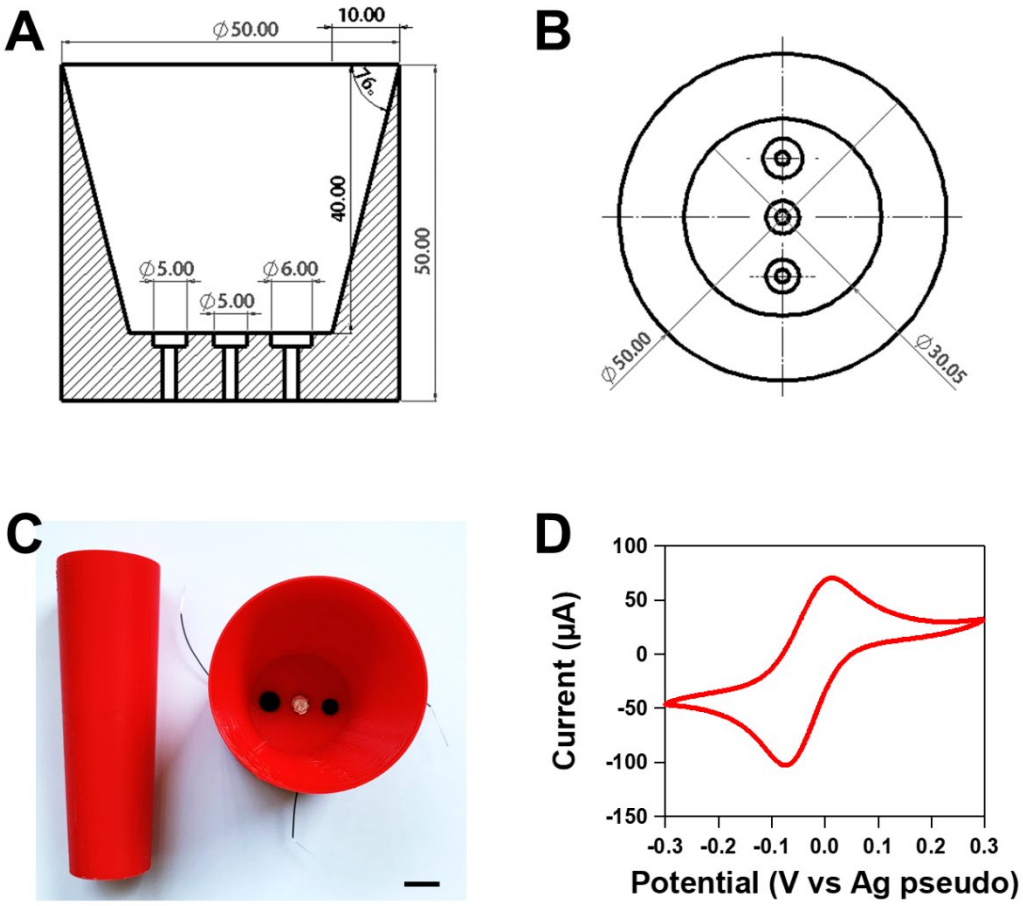

Figure 1. Design of the 3D printed electrochemical pestle and mortar. Where (**A**) and (**B**) showcase schematics of the PLA mortar device. (C) Photographs of the final 3D printed pestle and mortar, where the working and auxiliary electrodes were made using CB/PLA and the reference electrode was a silver painted CB/PLA electrode. The scale bar is 1 cm. (**D**) Cyclic voltammogram of 1mM hexaammineruthenium(III) chloride in 1M KCl at a scan rate of 100 mV/s.

Evaluation of the particle size of crushed tablets using the pestle and mortar

To evaluate the performance of the 3D printed pestle and mortar, the ability to crush a smaller melatonin tablet and larger vitamin C tablet was compared to a standard

laboratory pestle and mortar. Tablets were placed into the pestle and mortars, crushed and ground into powders for a duration of 1 minute. The powders then were collected and analysed for the particle size distribution. The powders which constituted of insoluble tablet excipients were suspended and sonicated in deionised water to ensure adequate dispersion. The wet mixture was then run in a Malvern Instruments Mastersizer (Malvern, UK) with a particle refractive index of 1.416, absorption index of 1.0 and dispersant refractive index of 1.33.

Electrochemical measurements using the pestle and mortar

Electrochemical measurements were carried out using a three-electrode system, which consisted of a silver pseudo reference electrode, a CB/PLA auxiliary electrode and a CB/PLA working electrode. All electrochemical experiments were carried out using a CH instrument potentiostat/galvanostat (CHI 630B; CH instruments, Texas). The electrochemical characteristics of the 3D-printed electrochemical mortar was assessed using 1 mM hexaammineruthenium(III) chloride in 1M KCl. Cyclic voltammograms were performed with a scan rate of 100 mV/s.

To characterise the 3D printed electrochemical pestle and mortar, 3 mg melatonin tablets (Nature's Bounty, UK) were utilised. These tablets were placed in the mortar, crushed, and ground into a fine powder, before being dissolved in 1 M KCl to make a 300 µg/mL solution using the pestle to stir. Differential pulse voltammetry (DPV) was utilised to measure the response of melatonin, where the pulse amplitude was 50 mV/s, the pulse width was 0.06 s, and the potential window was between 0 to +1.2 V. To compare the difference in the current response from tablets which were filtered and unfiltered, a

melatonin tablet was crushed to a fine powder using the 3D printed pestle and mortar and then was dissolved in 1 M KCl to make a 300 µg/mL solution and half of the solution was filtered using Grade 601 filter paper. Calibration responses were conducted using a 3 mg melatonin tablet and conducting serial dilutions of the tablet. Calibrations were conducted in the concentration range of 300 to 37.5 µg/mL. This approach was taken as we have previously shown that tablet excipients can reduce the current response of melatonin and other pharmaceutical active ingredients [38-40]. To evaluate the stability for repeated measurements of melatonin tablets, five repeated measurements were conducted using melatonin tablets. Following measurements, electrochemical treatment was used to regenerate the electrode using 0.5 M NaOH by holding the potential at +1.4 V for 20 s and then at -1.0 V for 20 s.

To evaluate the versatility of the pestle and mortar device, we conducted measurements with 75 mg Clopidogrel tablets (Torrent Pharma, UK) using DPV, 1000 mg ascorbic acid tablets (Holland and Barrett, UK) using CV and 500 mg paracetamol tablets (Boots, UK) using CV.

Performance of the electrochemical pestle and mortar to determine falsified tablets

Most falsified products reduce or remove the amount of the API by adding more cheaper bulking agents or utilising cheaper excipients [12]. We made falsified formulations which would mimic these factors. All falsified tablets were made using the original 3 mg melatonin tablets which were grinded down and mixed with different quantities of the binding agent lactose. The falsified compositions made contained 1.8 mg, 0.9 mg and 0.45 mg of melatonin. These tablets were assessed using the electrochemical pestle and

mortar and HPLC. The researcher conducting the electrochemistry and HPLC measurements were blinded to the composition of the falsified samples.

To conduct the HPLC measurements, we utilised the British Pharmacopeia assay for melatonin. Measurements were conducted using a PerkinElmer Flexar LC Autosampler HPLC system, in which the stationary phase was 15 cm × 4.6 mm octadecasilane (C18) 5 µm column (Sphereclone, Phenomenex) and the mobile phase consisted of 20 volumes of acetonitrile and 80 volumes of 0.245 % w/v solution of potassium dihydrogen orthophosphate (pH 3). The flow rate was 1.5 mL per minute and the injection volume was 10 µL. Measurements were conducted with a detector wavelength of 225 nm. Falsified tablet responses were compared to a calibration plot conducted in the range of 0.5 to 5 mg melatonin

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 Student t test or one-way ANOVA.

Results and Discussion

The 3D printed electrochemical mortar was initially characterised using the redox probe 1mM hexaammineruthenium(III) chloride in 1M KCl. **Figure 1D** shows a representative

cyclic voltammogram response from one mortar, where the inter batch variability was 2.8 % (n=5). This indicates that this approach to manufacturing the mortar can provide reproducible electrochemical devices.

Comparing the particle size of the crushed and grounded pharmaceutical tablets

The core function of a pestle and mortar is to crush and ground material into a fine powder and therefore we initially conducted experiments to evaluate the capabilities of our 3D printed pestle and mortar when compared to a standard laboratory pestle and mortar. We utilised two different tablet sizes to ensure that the pestle could crush larger and harder tablets. The melatonin tablet was small and easy to crush (see **supplementary video 1**) when compared to the vitamin c tablet (see **supplementary video 2**) which was a significantly harder tablet. In both cases, the tablets were crushed and ground into a powder for a duration of 1 minute and the particle size distribution was compared. **Figure 2A** shows the two different pestle and mortars used, the two tablets and resultant ground powder generated following 1 minute of activity.

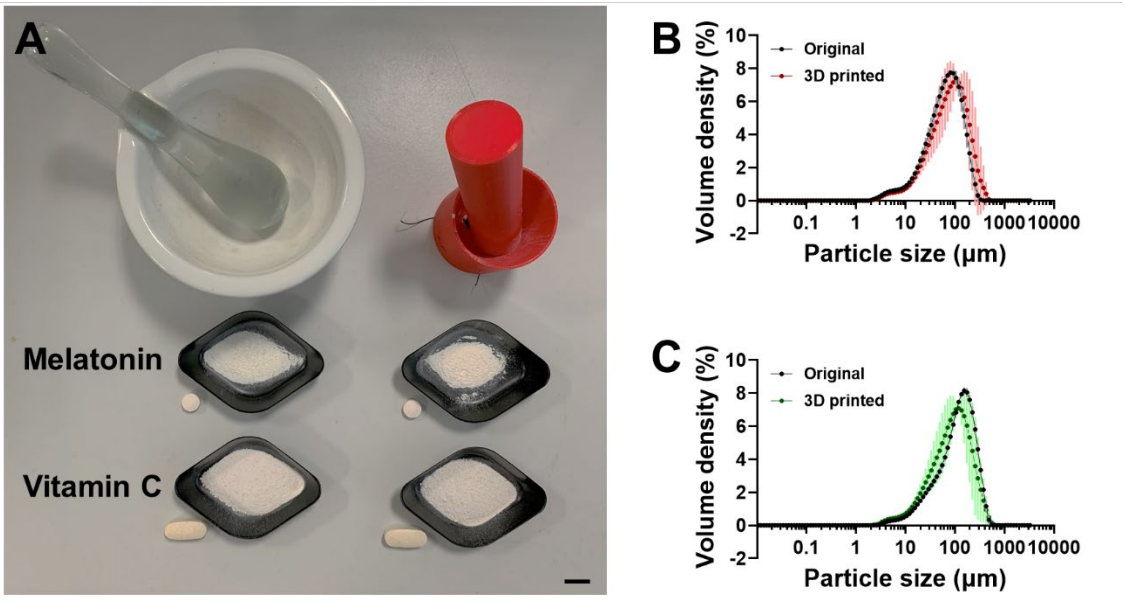

Figure 2. Evaluating the ability of the 3D printed pestle and mortar to crush and grind a pharmaceutical tablet. (**A**) Photograph showing the comparison of the powders generated from crushing and grinding a melatonin and vitamin C tablet using a standard laboratory and 3D printed pestle and mortar. Scale bar indicates 1 cm. Particle size distribution comparing the standard laboratory (labelled original) and 3D printed pestle and mortar for the powder generated for (**B**) melatonin and (**C**) vitamin C tablets. Data shown as mean ± st.dev., n=3.

The particle size distribution of tablet powders generated by the laboratory and 3D printed pestle and mortar were studied using a Mastersizer. **Figure 2B** & **C** shows the distribution of particle sizes present in the powders from the melatonin and vitamin C tablets. The particle

size analysis showed that the distribution was not significantly different in the standard laboratory pestle and mortar when compared to the 3D printed pestle and mortar for both the melatonin and vitamin C tablets (n=3). For melatonin tablets, the median particle size

by volume was 66 ± 6 μm on the laboratory pestle and mortar and 64 ± 6 μm for the 3D printed pestle and mortar. For vitamin C tablets, the median particle size by volume was 115 ± 8 μm on the laboratory pestle and mortar and 119 ± 6 μm for the 3D printed pestle and mortar. This greater median particle size on the vitamin C tablets was as expected, as more time is required to generate a fine powder when using a larger tablet size. Overall, the 3D printed electrochemical pestle and mortar under the same experimental conditions was able to crush and grind two different pharmaceutical tablets to the same capacity as a standard laboratory pestle and mortar.

Analytical performance of the 3D-printed pestle and mortar for determination of pharmaceutical tablets

To assay the analytical performance of the 3D printed electrochemical pestle and mortar, melatonin tablets were used. Given our emphasis to create a total analysis system, we conducted the measurement of the dissolved API in the presence of the insoluble excipients. Therefore, initially we compared the response of melatonin tablets filtered and unfiltered. **Figure 3A** shows DPV responses of a melatonin tablet where no difference was observed in the response between the filtered and unfiltered response. The oxidation peak potential of melatonin on the CB/PLA electrode was +0.75 V vs. pseudo-Ag reference electrode. **Figure 3B** shows the overall responses, where there was no significant difference in the current observed from filtered and unfiltered tablets (n=5). A greater spread in the responses were observed in the filtered samples, which is most likely due to sample preparation errors. These results indicate that measurements of melatonin tablets can be conducted in the presence of the excipients and thus reduce the

need for extra sample preparation steps allowing for total analysis. Our findings are identical to other studies which have shown that electrochemical measurements can be conducted in particulate solutions [38-40].

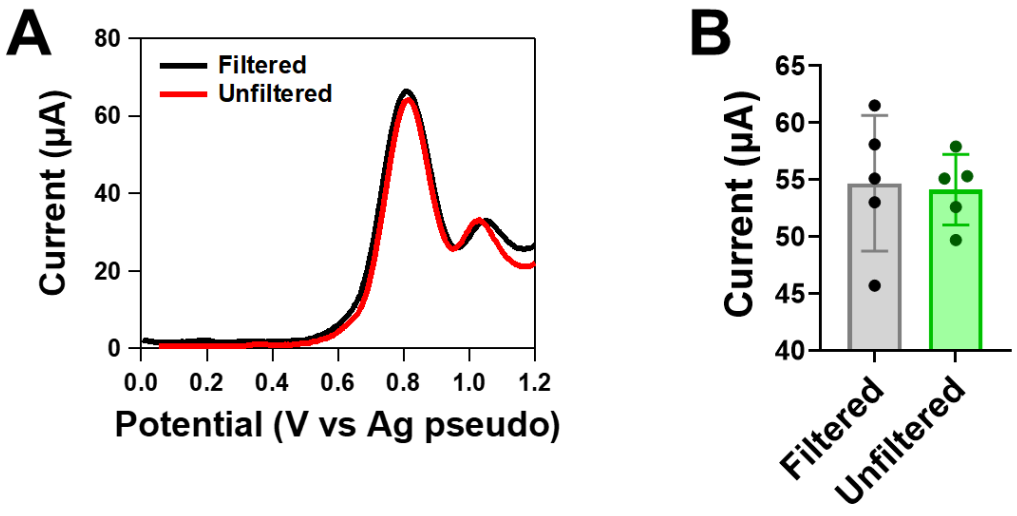

Figure 3. Comparing the responses of the melatonin tablet when filtered and unfiltered. (**A**) shows differential pulse voltammetry responses of melatonin tablets when measured on the 3D printed electrochemical pestle and mortar when using filtered and unfiltered solutions made using melatonin tablets. (**B**) Overall current responses from filtered and unfiltered solutions made from melatonin tablets. Data shown as mean ± st.dev., n=5.

Given our ability to clearly detect the presence of melatonin within the tablet without additional sample preparation steps, we conducted a calibration response in the presence of excipients. Given most falsified medicines and healthcare supplements contain little or no API, the ability to accurately monitor the concentration was essential. **Figure 4A** shows DPV responses where the current responses decreased when running concentrations

from 300 to 37.5 µg/mL. The calibration plot is shown in **Figure 4B** where the sensitivity was 0.2 ± 0.01 µA µg/mL^{-1} and the limit of detection was 7 µg/mL (n=5, LOD was calculated from 3 SDs of the y intercept using least-squares regression). No other studies have been conducted to monitor melatonin using 3D printed electrodes, however studies using boron-doped diamond or glassy carbon electrodes were able to observe smaller detection limits [38, 41, 42], but were not able to conduct these measurements as a total analysis system. The limit of detection and sensitivity of the 3D printed electrochemical mortar is suitable for measuring changes in the concentration of tablets and thus has the potential to be suitable to identification of falsified medicines and healthcare supplements.

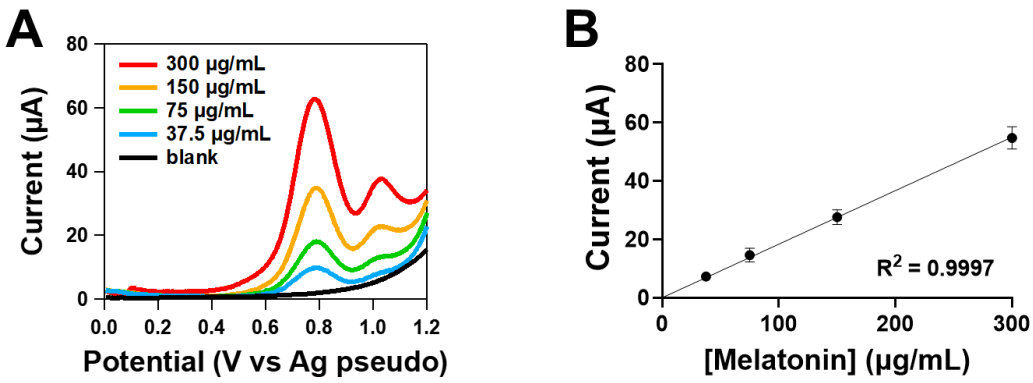

Figure 4. Calibration response of melatonin. (**A**) differential pulse voltammetry responses for varying concentrations of melatonin made using serial dilutions of the melatonin tablet. (**B**) Calibration plot showing a linear relationship between concentration and current, where the

oxidation peak current was measured at +0.75 V vs. pseudo-Ag reference electrode. Data shown as mean ± st.dev., n=5.

Our 3D printed electrochemical pestle and mortar provided the ability to conduct sample preparation and accurate analysis of concentration in one step making this a total analysis system for pharmaceutical tablet measurements. **Supplementary video 3** showcases the entire process from start to finish, with one individual measurement taking around 3 minutes, in which the limiting step is the time taken for the DPV measurement.

To showcase the breadth of the device, we assessed the ability to determine other pharmaceutical oral formulation products and use an alternative electroanalytical technique. **Figure 5** shows current responses for different pharmaceutical tablets and healthcare supplements. **Figure 5A** shows the response of vitamin C on the CB/PLA electrode, conducted using CV, where the oxidation peak potential was +1.05 V. Recently there has been an upsurge in the purchase of vitamin C during the COVID19 pandemic [43, 44], which has made this dietary nutrient a suitable target for falsification [45]. **Figure 5B** shows the response of clopidogrel on the CB/PLA electrode, conducted using DPV, where the oxidation peak potential was +0.8 V. Clopidogrel also commonly sold under commercial name Plavix® is a frontline anti-platelet medicine, which helps prevent platelets from sticking together and forming a dangerous blood clot. Production of falsified clopidogrel medication has recently occurred in Europe and the USA, where patients were given ineffective “Plavix” tablets leading to complaints from patients and subsequent testing showcased that the product was falsified [46, 47]. **Figure 5C** shows the response of paracetamol on the CB/PLA electrode, conducted using CV, where the oxidation peak

potential was +1.15 V. The oxidation of paracetamol was previously shown on a 3D printed carbon-loaded acrylonitrile butadiene styrene electrochemical cell-on-a-chip device, highlighting the potential for simple on-site analysis [31].

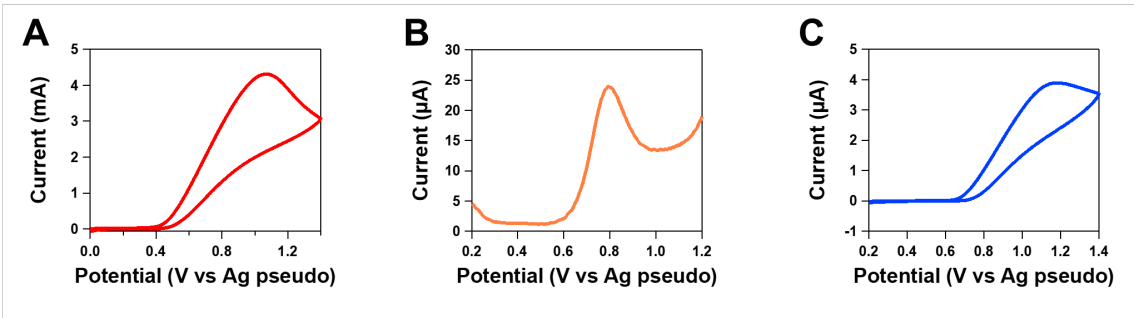

Figure 5. Determination of various medicines and healthcare supplements. Cyclic voltammograms of (**A**) 5mg/mL vitamin C in 1 M KCl, (**B**) 1 mg/mL clopidogrel in pH 3 acetate buffer and (**C**) 2.5 mg/mL paracetamol in 1 M KCl.

Overall, our device shows potential for monitoring a host of drugs known to be falsified, however electrochemical detection is not feasible for all falsified drugs and thus this approach to detection at present is limited to only easily oxidisable substances. Modifications of the electrodes using chemical or biological entities that provide selective detection may however broaden the scope of this 3D printed electrochemical pestle and mortar to all widely falsified drugs.

Repeatability and regeneration studies for repeated measurement of melatonin tablets

We explored the ability of the 3D printed pestle and mortar to conduct repeated measurements of single tablets and thus understand the usage potential of the device. **Figure 6A** shows 5 repeated measurements conducted on melatonin tablets, where there was a gradual reduction in the current with successive measurements. The results from repeated studies are shown in **Figure 6B**, where following the first measurement there was a signficant reduction in the oxidation peak current from measurements 2 to 5 ($p<0.01$, $n=5$). Melatonin oxidation products have been shown to electropolymerize in solution [42], which can lead to strongly adsorbed products that foul the electrode surface. Therefore, measurements of melatonin tablets and most other drugs and healthcare supplements are limited to single use. Although the device is made with mostly biodegradable materials making it viable for single use, studies were conducted to explore if electrochemical treatment [36, 37] can be used to regenerate a fouled CB/PLA electrode surface. **Figure 6C** shows the original response of 300 µg/mL melatonin and that following regeneration after exposure to five repeated measurement, showing the success of the regeneration process to recover the response. **Figure 6D** shows the original response of 1mM hexaammineruthenium(III) chloride in 1M KCl and that following electrochemical regeneration after exposure to five repeated measurement of melatonin tablets. There was no significant difference in the cathodic peak potential (ipC, **Figure 6E**, $n=5$) and difference in the cathodic and anodic peak potential (ΔE, **Figure 6F**, $n=5$) when comparing the original response and that following electrochemical regeneration. This indicates that electrochemical treatment can effectively clean the CB/PLA electrode surface, overcoming effects of electrode fouling and thus providing the ability to conduct multiple repeated measurements on the 3D printed electrochemical mortar.

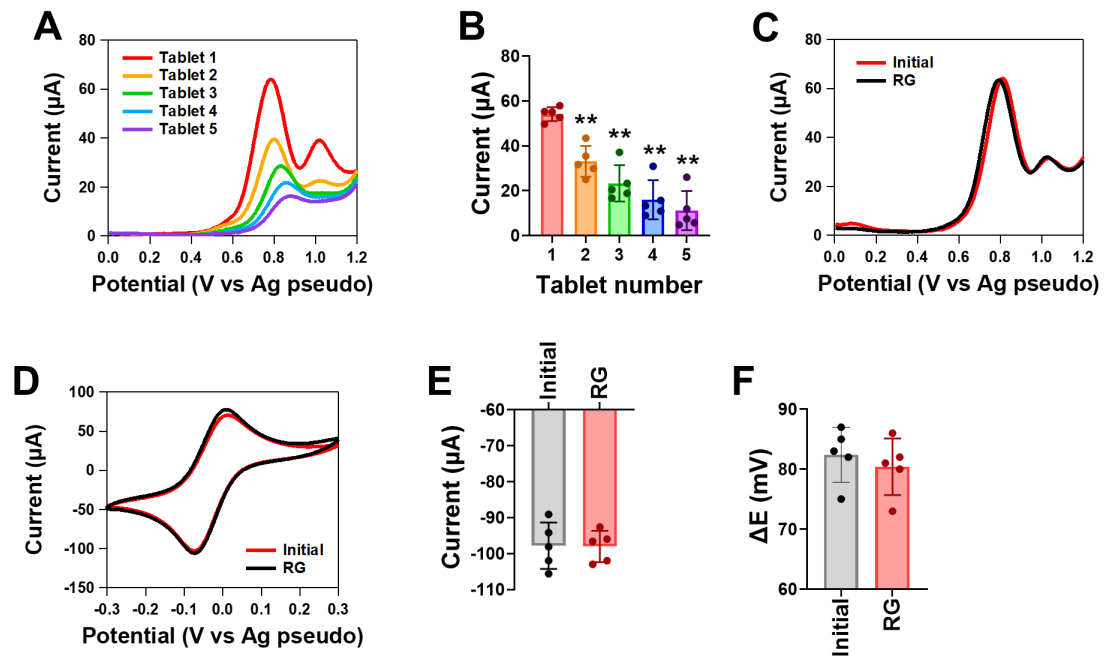

Figure 6. Repeatability and electrode regeneration studies. (**A**) Differential pulse voltammograms of repeated measurements of melatonin tablets. (**B**) Overall current responses observed when repeated measurements of melatonin tablets were conducted. Due to the reduction of the current following repeated tablet measurements, electrochemical treatment regeneration studies were conducted. (**C**) DPV response of 300 μg/mL of melatonin prior to tablet measurements and following electrochemical treatment after conducting 5 measurements in melatonin tablets. (**D**) Cyclic voltammograms of 1mM hexaammineruthenium(III) chloride in 1M KCl conducting prior to tablet measurements and following electrochemical treatment after conducting 5 measurements in melatonin tablets. Comparison of the anodic peak current (**E**) and ΔE (**F**) from the initial response and following electrochemical regeneration (RG). Data shown as mean ± st.dev., n=5, where **p<0.01.

Studies were conducted to explore the robustness of the pestle and mortar device using the regeneration protocol for repeated measurements. **Supplementary Figure 1** shows

10 repeated response of 300 µg/mL melatonin where the device was regenerated in sodium hydroxide in-between each response. There was no signficant difference in the responses observed showcasing the ability of the regeneration to allow for multiple measurements to be conducted. During these measurements, each time the melatonin tablet was crushed and ground into a powder, which also may impact the integrity of the electrodes at the base of the pestle. **Figure 7** shows the impact of multiple crushing and grinding on the electrodes within the pestle. No noticeable difference was observed after 10 preparations on the electrodes, but after 20 preparations, some of the silver paint on the reference electrode was removed. Although this was removed, this did not impact the ability to measure the melatonin response. Even though there is potential for multiple measurements through regeneration, the main purpose of use is for identification of falsified medicine where potential contamination between measurements would hinder appropriate quality control measures and thus this device is best suited as single use.

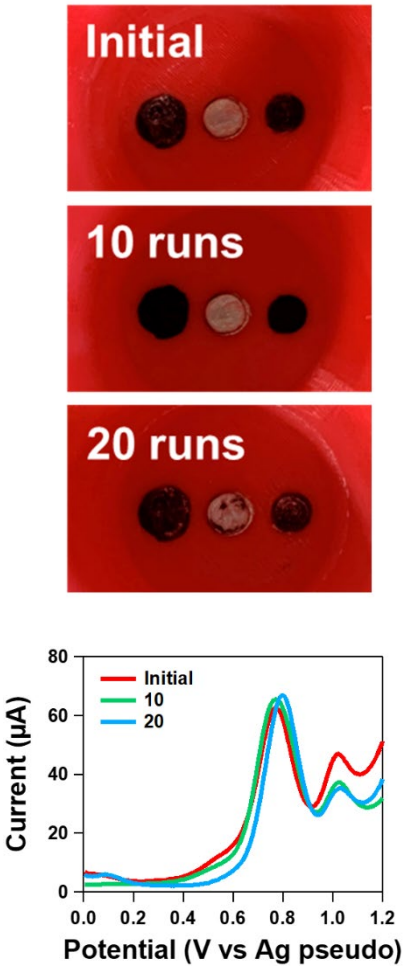

Figure 7. Investigating the robustness of the 3D printed electrochemical pestle and mortar. Photographs show the original device and following 10 and 20 runs of crushing and grinding a melatonin tablet. The differential pulse voltammograms of 300 µg/mL after 10 and 20 uses of the pestle and mortar were compared to the original response.

Analysis of falsified melatonin tablets

To assess the suitability of our 3D printed electrochemical pestle and mortar, measurements of falsified medicines were conducted. The compositions of three falsified tablets, which were made in the laboratory, were blinded to the researcher conducting the

electrochemical and HPLC measurements. **Figure 8A** shows the response from 300 µg/mL original melatonin tablet and three falsified tablets. In each case there was a reduction in the current observed at the peak potential for melatonin. Additionally in falsified tablet 2, we observed an additional oxidation peak at 0.65 V, which may be due to effect of lactose, which is the only additional component added. The overall current responses for the falsified tablets are shown in **Figure 8B**, where there is a signficant reduction in the current observed in falsified tablet 1-3 when compared to the original tablet ($p<0.01$, $n=3$). These findings highlight that the 3D printed electrochemical pestle and mortar can identify falsified medicines and healthcare supplements. **Table 1** compares the accuracy of the 3D printed electrochemical pestle and mortar with HPLC. Given that the composition of the three falsified tablets is known, the percent recovery of melatonin can be obtained. When using the 3D printed pestle and mortar, the recovery values are within the range of 101 to 105 %, showcasing excellent accuracy in determining the concentration of melatonin. These values are not significantly different from those obtained from HPLC, in which the recovery observed was from 101 to 99 %. However, the HPLC responses observed were more precise than those obtained using the 3D printed electrochemical pestle and mortar.

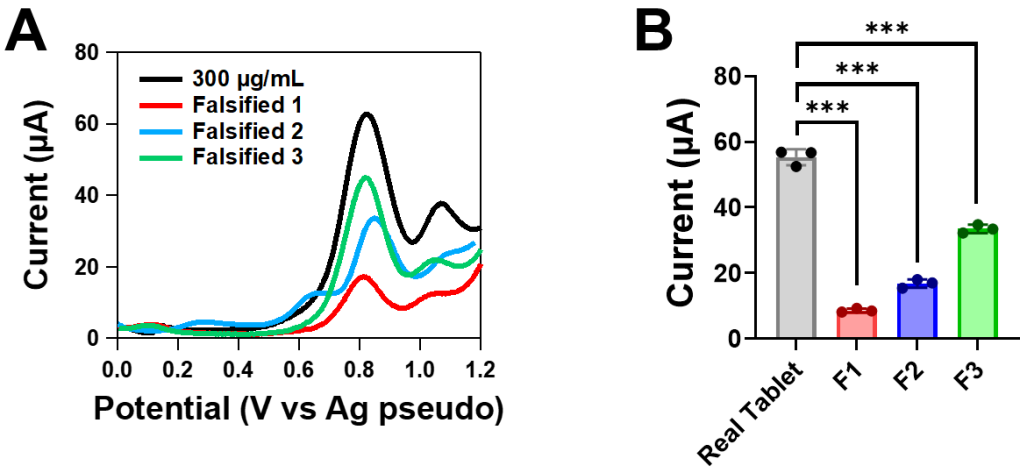

Figure 8. Determination of in-house made falsified melatonin tablets. (**A**) shows differential pulse voltammograms of an original tablet response at 300 µg/mL against three different falsified tablets. (**B**) Overall changes in the current response of melatonin for the original tablet and falsified tablets. Data shown as mean ± st.dev., n=3, where ***p<0.001.

Table 1. Analysis of the percentage recovery of melatonin in falsified tablet samples using the 3D printed electrochemical pestle and mortar and HPLC

		3D electrochemical pestle and mortar		HPLC	
Sample	Amount present (mg)	Amount Found (mg)	Recovery (%)	Amount Found (mg)	Recovery (%)
Falsified tablet 1	**0.45**	**0.47 ± 0.03**	**105**	**0.457 ± 0.004**	**101.5**
Falsified tablet 2	**0.90**	**0.92 ± 0.07**	**102**	**0.901 ± 0.004**	**100.0**

Falsified tablet 3	**1.80**	**1.83 ± 0.07**	**101**	**1.788 ± 0.003**	**99.26**

These results have highlighted that our device is successfully able to monitor the API concentration in medicines and healthcare supplements. However, like any analytical approach, electrochemical detection has limitations, where substances with a similar chemical structure could be oxidised at the same voltage as melatonin can cause interference and falsely indicate that melatonin might be present within the tablet.

Conclusions

This study has developed and demonstrated a simple total analysis system for the determination of falsified medicines and healthcare supplements using a 3D printed electrochemical pestle and mortar. A CB/PLA working electrode was embedded into the base of the PLA printed mortar using a 3D printing pen. The 3D printed pestle and mortar was able to crush and grind a tablet to a fine powder to the same consistency as a standard laboratory pestle and mortar. Using melatonin tablets to characterise the device, it was feasible to accurately monitor the amount of melatonin in the presence of insoluble excipients. Following electrochemical treatment, the CB/PLA electrode can be regenerated allowing for subsequent analysis. In a blinded study, our 3D printed electrochemical pestle and mortar was comparable to HPLC in successfully identifying the amount of melatonin present in falsified tablets. Our findings clearly highlight that the 3D electrochemical pestle and mortar is a unique total analysis system that provides

accurate and rapid determination of falsified drugs. This device is manufactured to be environmentally friendly and is suitable for remote pharmaceutical analysis.

Statements and Declarations

Competing Interests: The authors have nothing to declare

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