

# Voltammetric quantification of acetylsalicylic acid in pharmaceutical formulations utilizing copper wire electrode

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**Abstract:** This research describes the quantitative detection of acetylsalicylic acid (ASA) as salicylic acid (SA) in pharmaceutical formulations using electrochemical determination at copper electrode. The cyclic voltammetry (CV) technique was applied to investigate the electrochemical behavior of salicylic acid at a copper electrode. The anodic peak of salicylic acid (SA) was obtained at  $\sim 0.6V$  vs. Ag/AgCl quasi electrode in a phosphate buffer solution of pH 11.5. The measurement was made in a potential range of 0.00V to 0.80V, where all the reported potentials are referred to this reference electrode. The oxidation peak current was linearly dependent on the concentration of salicylic acid, which ranges between 0.05mM and 15mM with a detection limit of 14.9 $\mu$ M. Three different pharmaceutical formulations from three different brands were successfully analyzed for acetylsalicylic acid using the newly developed method. The acquired results and the indicated values had an RSD% of less than 2.02, which was in good agreement with the concentration of real samples.

**Keywords:** Salicylic acid, voltammetry, copper electrode, pharmaceutical formulations.

## INTRODUCTION

Acetylsalicylic acid (ASA) or aspirin, the well-known drug for more than 140 years, was introduced as an anti-inflammatory drug and still attracts distinct attention due to its clinical benefits for the treatment of inflammation, fever, renal function, and platelet aggregation (Fijakowski *et al.*, 2022). Many studies have demonstrated the therapeutic benefits of aspirin when administered in specific dosages. Aspirin has a revealed effect on cardiovascular diseases, cancers, and even the occurrence of Alzheimer's disease (Fijakowski *et al.*, 2022). ASA has an antioxidant influence as well (Abdulmajeed *et al.*, 2021). Aspirin, however, has shown to have a number of adverse effects in the gastrointestinal (GI) tract (Li *et al.*, 2020).

A variety of analytical techniques have been applied for the quantification of acetylsalicylic acid, including high-performance liquid chromatography (HPLC) (Kim *et al.*, 2018), colorimetric (Liang *et al.*, 2020), UV-Vis spectrometry (Daci *et al.*, 2020), and spectrofluorimetry (El-Olemy *et al.*, 2021). The use of electrochemical techniques is widespread because of their exceptional merits of low cost, ease of setup and speedy analysis time with distinctive analytical performance (Tran *et al.*, 2022).

Metal electrodes were used in electrochemical analysis with and without surface modification. Although rare earth elements, like platinum, are frequently used as an electrode. Researchers are looking for more affordable and environmentally friendly alternatives due to the high

cost and toxicity of chemicals (Kovendhan *et al.*, 2019). Many metals and alloys have long been investigated for use as electrode materials in various mediums (Kovendhan *et al.*, 2019). The catalytic performance of copper electrodes is comparable to that of carbon-coated noble metal cathodes and they are inexpensive and have a wide surface area (Kovendhan *et al.*, 2019). Among its many unique electrocatalytic properties, copper exhibits great activity for the electrochemical reduction of nitrate and carbon dioxide (Yu *et al.*, 2022, Chen *et al.*, 2023). Copper is one of the most active electrode materials for nitrate reduction. Therefore, a number of recent electrochemical studies on Cu single crystals have been conducted in an effort to link the catalytic activity to the atomic surface structure (Scholten *et al.*, 2021). For electroanalysis, copper electrodes were either used immediately or after surface modification. A low-cost copper wire (Cu-wire) electrode made of copper nanoparticles was developed in order to identify the chemical oxygen demand in water (Elfeky *et al.*, 2022). Additionally, Velasco-Medina *et al.* modified copper electrodes with AgHg or AgBi bimetallic particles on copper electrodes coated with a Nafion (Nf) film. The electrodes were capable of direct, precise and sensitive detection of synthesized peptides (Velasco-Medina and Espinoza-Montero., 2019). Tarantseva *et al.* used copper electrode for the amperometric determination of ethanol in beverages in alkaline solutions (Tarantseva *et al.*, 2021). Roushani *et al.* used a copper electrode for hydrogen peroxide determination (Roushani *et al.*, 2019). Maria *et al.* utilized a copper electrode for the spectroelectrochemical determination of trichloroacetic acid (Escalpez *et al.*, 2011). Mohammad *et al.* developed a new pharmacokinetic method using a copper electrode

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for the electrochemical determination of adrenaline (Mohammad *et al.*, 2011).

Numerous investigations have examined the electro-oxidation of copper electrodes in alkaline environments using a variety of techniques (Bodappa *et al.*, 2019). In this electrochemical process, the hydroxide content and the earlier creation of a specific layer of Cu (II) oxide are both significant variables (Bodappa *et al.*, 2019). Copper electrodes work well in alkaline medium in anodic processes connected to a variety of organic compounds, and this has been attributed to the involvement of the Cu(III) species as an electron-transfer mediator. The neutralization of the protons produced during the creation of the CuO(OH) active sites by water release depends on the hydroxide ions. The rate of bridging intermediate formation is anticipated to be slower at low hydroxide concentrations due to the slower active site development (Elfeky *et al.*, 2022). On the anodic peak potential of the Cu/CuO electrode, the effect of NaOH content in the range of 0.05 to 0.5 M was evaluated. The highest current increased up to 0.1 M of NaOH concentration. A 0.1 M NaOH solution was found to have the finest voltammetric profile with a clearly defined peak potential and was therefore selected for further study (Dai *et al.*, 2018).

Every method has benefits and drawbacks because it can be applied to different analytical needs. However, due to its inherent advantages of simplicity, high sensitivity, and low cost, the use of electrochemical sensors is recommended as a promising alternative strategy for the detection of electroactive species (Amayreh *et al.*, 2021, Amayreh *et al.*, 2021). The purpose of this research was to use copper electrodes to create a novel, quick, sensitive and easy method for electrocatalytically measuring salicylic acid in pharmaceutical formulations based on the hydrolysis of acetylsalicylic acid into salicylate in basic solution.

## MATERIALS AND METHODS

### *Chemicals and reagents*

From the Merck chemical company, salicylic acid was obtained (Darmstadt, Germany). 0.1M Na<sub>2</sub>HPO<sub>4</sub> and 0.1M NaH<sub>2</sub>PO<sub>4</sub> were combined in equal amounts to create phosphate buffer solutions (PB) with various pH values. To change the pH levels, a 0.1 M NaOH solution was used. The only purification that was performed on any of the chemicals was to ensure that they were of analytical quality. Salicylic acid was dissolved in Millipore-MilliQ water to create a stock solution (15mM), which was then kept at 4°C. The stock solutions were successively diluted in PB solution with a pH of 7 to create other diluted standard solutions, 10, 5, 2.5, 1.0, 0.5, 0.1, and 0.05mM. The creation of each solution involved using a high purity water system (Millipore-MilliQ). From the International

Jordanian Company, the nitrogen gas was G5® quality (99.999% pure).

### *Apparatus*

Using a potentiostat (PAR model 362, EG & G) connected to a computer via GPIB interface (IEEE), cyclic voltammetry (CV) was performed. Software called Labview® (IEEE) that was locally modified was used for data collection. A one-compartment system comprising three electrodes was used for the electrochemical analysis. The working electrode was a piece of 99.99% minimal purity certified reagent copper wire from Aldrich, measuring 1.0 mm. The auxiliary electrode was a 1.0 mm polycrystalline platinum wire with a 99.99% minimum purity guarantee from Aldrich. All potential measurements in this work were performed with a quasi-reference electrode made of an Ag/AgCl electrode (QRE). Due to the numerous benefits of the quasi-Ag/AgCl electrode, including its ease of preparation and use, absence of ohmic resistance, liquid junction, and lack of electrode contamination (Alnoush *et al.*, 2021).

The cell was supplied with inlets and outlets for nitrogen gas purging and blanketing. The surface area of the working electrode was kept constant by curving the end of the electrode to take a U-shape. The shorter part of the wire was touching the meniscus of the surface from underneath the surface of the solution. A laboratory-made quasi-Ag/AgCl electrode was used as a reference electrode, and all the reported potentials are referenced to this electrode.

### *Cu/CuO electrode preparation*

The copper electrode had to be ready for the electrochemical studies by being polished with alumina and thoroughly washed with distilled water and then immersed in the single compartment electrochemical cell containing degassed 0.1M. In order to obtain the defined features of the copper cyclic voltammogram, which reflect the cleanliness of the electrode surface and either electrochemical system, the copper electrode was then activated by cyclizing in the alkaline medium (0.1M NaOH) over the potential window from -1.0 V to +0.8V as shown in Fig. 1.

### *Methodology*

The cyclic voltammetry technique was used for the purpose of developing and validating a new electrochemical method for the analysis of acetylsalicylic acid as salicylic acid after the hydrolysis using 0.1M NaOH. The method implies investigating the electrochemical response of salicylic acid at the copper electrode surface in basic solution (0.1 M NaOH) to avoid copper electrode corrosion. Based on the recorded cyclic voltammograms of salicylic acid(SA) standard solutions, the oxidation peak of SA was considered as the electrochemical signal for method development, where

this system was considered as an irreversible system. Then the following parameters were carried out for method development and validation: (a) determine the effect of pH on the recorded current and potential of 5.0 mM salicylic acid at a constant scan rate of 50 mV/sec; (b) investigate the relationship between the roots of the scan rates (5,10, 20, and 50mV/sec) and the obtained current to make sure that the system is under diffusion control conditions; (c) the linearity of the method was investigated by studying the relationship between various concentrations of standard solutions (0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10, and 15 mM) and the recorded current;(d) The sensitivity of the method was determined by constructing a calibration curve. The slope of the curve represents the sensitivity. Additionally, the limits of detection (LOD) and quantitation (LOQ) were calculated to provide quantitative measurement for the method's ability to detect and quantify analytes at low concentrations. The LOD is determined as three times the standard deviation of the blank signal divided by the slope, while the LOQ is typically calculated as ten times the standard deviation of the blank signal divided by the slope; (e) the inter- and intra-day precision was evaluated by reporting current values of standard solutions containing 1, 2, 5, and 10 mM salicylic acid intraday and interday; (e) the selectivity of the copper electrode toward salicylic acid was tested by studying the influence of specific substances, including organic molecules like ascorbic acid and hydroquinone and inorganic ions like  $K^+$ ,  $Na^+$ ,  $Ca^{2+}$ ,  $Zn^{2+}$ ,  $Mg^{2+}$ ,  $Al^{3+}$ ,  $Cu^{2+}$  and  $Fe^{2+}$ ; ( f) recovery was tested by spiking the extract of pharmaceutical formulations with 2.50, 4.26, and 5.60mM salicylic acid; (g) the standard addition method was used to determine the concentration of salicylic acid in the collected pharmaceutical formulation samples.

### Sample preparations

Pharmaceutical formulation samples of acetylsalicylic acid, Salisal<sup>®</sup>100 (Jordan), Aspitect<sup>®</sup>81 (USA), and Aspirin<sup>®</sup> protect100 (Germany) were purchased from Jordanian pharmacies. The acetylsalicylic acid (ASA) content of the chosen brands of pharmaceutical formulations was examined. Each brand's tablet was well crushed in a porcelain mortar and transferred to a 50.0 mL beaker and dissolved with 25.0 mL of buffer solution pH 11.5 PB, where acetylsalicylic acid is hydrolyzed to form salicylic acid in a highly alkaline solution (Jawad *et al.*, 2023).

The sample's solution was subjected to 10-minute intervals of sonication and equilibration. Then it was filtrated using a 0.45-μm Millipore filter, transferred and diluted to the desired volume in a 100 mL volumetric flask. The stock solutions were kept at a 4°C temperature for subsequent analyses. A volume of 10.0 mL of solution was introduced to the electrochemical cell. The solution was kept in a nitrogen gas atmosphere after being

de-aerated with nitrogen gas for five minutes before the voltammetric experiments. The solutions of the commercial tablets were voltammetrically analyzed to determine their ASA concentration on a copper electrode with a potential range of 0.0 to 0.8 volts.

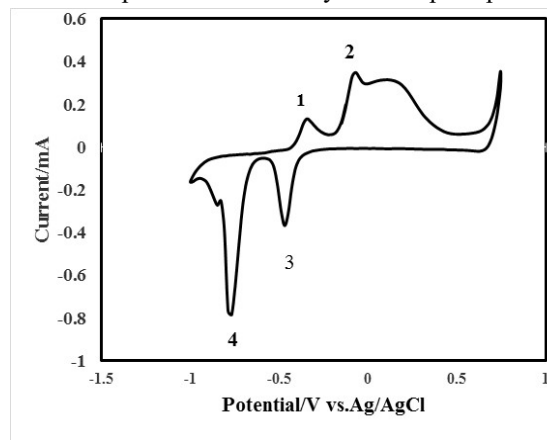
## STATISTICAL ANALYSIS

The experiments were all carried out in triplicate. Utilizing Microsoft Excel 2010, statistical analyses were performed. For each cyclic voltammogram, the oxidation peak current was isolated and plotted versus concentration to create the standard curves using linear regressions. The means and standard deviations of the data were used to express them.

## RESULTS

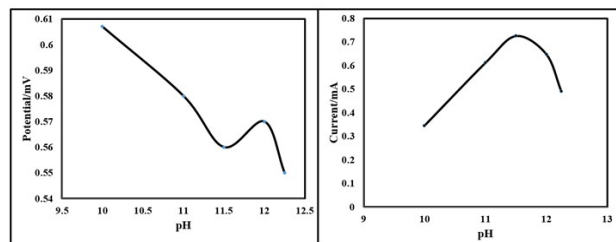
### Voltammetric studies and method validation

In this section, copper-wire electrode was electrochemically characterized in a solution of 0.1M NaOH. The cyclic voltammogram shown in Fig. 1 is an example of the typical current-voltage achieved for the copper electrode in a 0.1M NaOH solution (Balkis *et al.*, 2018). The primary characteristics of the captured cyclic voltammograms, which are made up of four peaks, show how clean the copper electrode surface is and how ready it is for additional electro analysis experiments. Anodic peak 1 represents the production of a first layer of copper (I) oxide ( $Cu_2O$ ), and anodic peak 2 the formation of a second mixed layer of copper (II) oxide and copper (II) hydroxide ( $CuO/Cu(OH)_2$ ). When 0.70 V vs. Ag/AgCl is reached, Cu (II)/ Cu (III) oxidation has occurred. The cathodic peaks 3 and 4, which correspond to the  $Cu(II)/Cu(I)$  (0.55 V vs. Ag/AgCl) and  $Cu(I)/Cu(0)$  (0.84 V), could be seen by looking at the reverse scan (Elfeky *et al.*, 2022). Up to a concentration of 0.1 M of NaOH, the peak current rose. As a result, a 0.1M NaOH solution was chosen for additional research since it had the best voltammetric profile and a clearly defined peak potential.



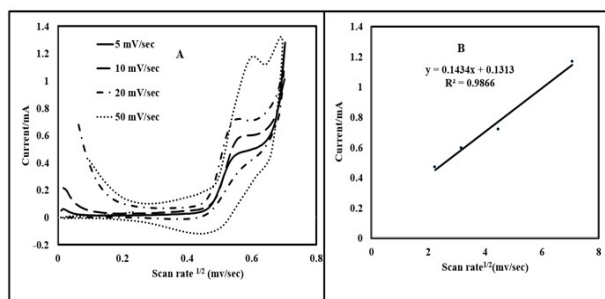
**Fig.1:** Cyclic voltammogram of copper wire electrode in 0.1M NaOH, Scan rate=50mV /sec

At pH levels between 10.0 and 12.25, the impact of pH on the anodic peak current and peak potential of salicylic acid at the copper electrode was investigated. The maximum anodic peak current was attained at pH 11.5, as shown in Figs. 2a and 2b. While there is no discernible impact of pH on the oxidation peak potential, where the peak potential ranges between 0.55 and 0.61 V.



**Fig. 2:** Plot of (a) oxidation peak current versus pH and (b) peak potential versus pH for 5.0mM salicylic acid prepared in 0.1M PB solution at copper electrode Scan rate=50 mV/sec.

The relationship between scan rate and the anodic peak current of salicylic acid at various scan rates was investigated. Fig. 3 shows a plot of the anodic peak current of salicylic acid vs. the square root of scan rate. It is evident from the curve that there is excellent linearity between the current of the anodic peak current of salicylic acid and the square root of scan rate ( $R^2=0.9866$ ).



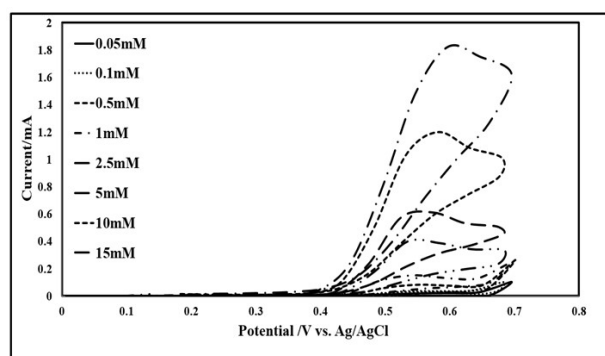
**Fig. 3:** (a) Cyclic voltammograms of copper electrode at scan rates of 5, 10, 20 and 50 mV/s in 10 mM salicylic acid solution prepared in 0.1 M PB solution, pH=11.5. (b) The relationship between the current of salicylic acid oxidation signal vs. the square root of scan rate.

Fig. 4 shows copper electrode cyclic voltammograms for several common salicylic acid solutions. Salicylic acid concentrations between 0.05 mM and 15.0 mM provide a linear and wide dynamic range when the anodic peak current is plotted against the concentration. The calibration equation is given by  $i_p(\mu A) = 0.1198C_{SA} + 0.0249$  and the calibration curve (Fig. 5) displays exceptional linearity with a determination coefficient of  $R^2=0.9959$ .

The current values for standard solutions containing 1, 2, 5, and 10 mM salicylic acid were extracted to evaluate the inter- and intra-day precision. For ten subsequent

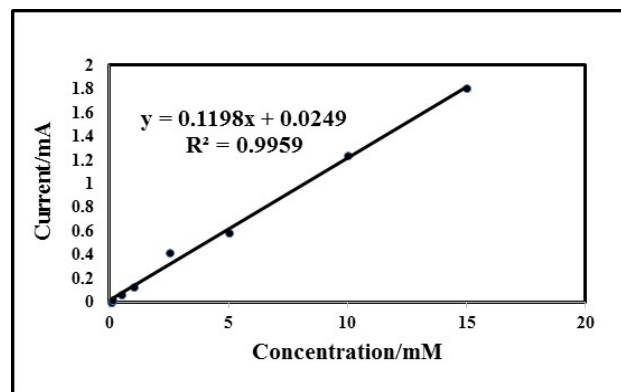
determinations of each concentration, the relative standard deviation (RSD) was found to be between 1.93 and 8.10%.

The detection limit value (based on  $S/N=3$ ) and the quantitation limit (based on  $S/N=10$ ) were 14.9 $\mu$ M and 45.1 $\mu$ M, respectively.

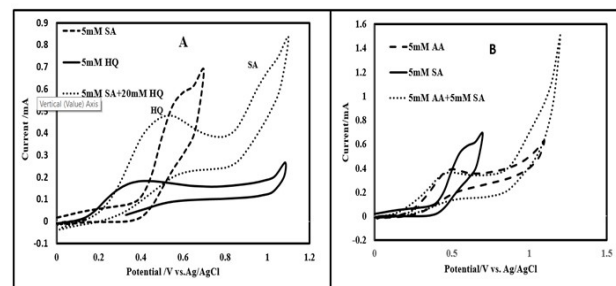


**Fig. 4:** Cyclic voltammograms of copper electrode in a PB solution pH 11.5 containing 0.05,0.1,0.5,1.0,2.5,5.0, 10, and 15mM of salicylic acid. All the scans were recorded at a scan rate = 50 mV/sec

Where  $i_p$  is the anodic peak current and  $C_{SA}$  is the concentration of salicylic acid.



**Fig. 5:** Calibration curve for the measurement of salicylic acid for various concentration (0.05-15mM) using a copper wire electrode.



**Fig. 6:** Cyclic voltammograms of a copper wire electrode in(a) (---)5.0mM SA,(—)5.0 mM HQ, and (...). 5.0 mM SA+5.0 mM HQ.(b) (---)5.0 mM SA,(—)5.0 mM AA, and (...). 5.0 mM SA+5.0 mM AA scan rate, 50 mV/sec.

**Table 1:** Recoveries salicylic acid from spiked pharmaceutical formulations obtained by the developed method.

Samples	Content of salicylic acid (mM)	Spiked salicylic acid (mM)	Detected salicylic acid after addition (mM)	Recovery(%)
Salisal®100	5.50	2.50	8.10	103.89±3.35
AspItect®80	4.49	4.26	8.49	93.97±2.23
Aspirin®100	5.50	5.60	10.87	95.85±3.74

**Table 2:** Acetylsalicylic acid content in pharmaceutical formulations collected from the Jordanian local pharmacies as determined by cyclic voltammetry using copper wire electrode.

Pharmaceutical formulation	Actual mass(mg) of acetylsalicylic acid/tablet	Conc.(mM) of SA after ASA hydrolysis with PB(pH=11.5)/tablet	Average of determined Conc(mM) of SA/tablet(n=3)	RSD(%)
Salisal®100	100	5.50	5.58	1.99
Aspirin®100	100	5.50	5.65	2.02
Aspitect®80	80	4.49	4.47	0.95

### Potential interference

The influence of specific substances, including organic molecules like ascorbic acid and hydroquinone and inorganic ions like  $K^+$ ,  $Na^+$ ,  $Ca^{2+}$ ,  $Zn^{2+}$ ,  $Mg^{2+}$ ,  $Al^{3+}$ ,  $Cu^{2+}$ , and  $Fe^{2+}$ , was assessed in order to evaluate the copper wire electrode's selectivity. While  $Na^+$  and  $K^+$  did not exhibit any response toward a copper electrode, none of the aforementioned inorganic ions did. These hydroxides were insoluble in a basic solution. While hydroquinone and ascorbic acid revealed a clear response to copper electrode.

Investigations were made into the interference caused by phenolic chemicals, such as hydroquinone. Salicylic acid and hydroquinone's oxidation peaks are depicted in Fig 6-a. Fig. 6-a shows that there are two distinct peaks for the two chemicals, and these peaks did not combine until there was a significant amount of hydroquinone present (four folds or higher of the concentration of salicylic acid). While Fig. 6-b depicts the ascorbic acid and salicylic acid oxidation peaks, no interference is seen when the ascorbic acid concentration is the same as that of the salicylic acid.

### Recovery

The validity of the developed voltammetric method for acetylsalicylic acid detection was examined for three pharmaceutical samples. A standard solution of salicylic acid of known concentration, 15.0mM, was spiked into the samples to evaluate the percentage recovery. As shown in Table 1, the recoveries for the spiking of 2.50, 4.26, and 5.60mM salicylic acid in the solution of pharmaceutical formulation samples range between 93.97 and 103.89%.

### Pharmaceutical formulations analysis

The effectiveness of the developed and validated voltammetric approach was assessed for the detection of acetylsalicylic acid in three genuine samples with low-

complexity pharmaceutical tablet matrices. Acetylsalicylic acid was quantified using the conventional standard addition method. Table 2 lists the consequences of the voltammetric approach established to analyze these pharmaceutical formulations.

## DISCUSSION

The potential is very stable at a high pH because the selectivity of the copper electrode for salicylate versus  $OH^-$  is high (Martynov, Naumova *et al.*, 2016). As a result, pH 11.5 was chosen as the ideal pH of phosphate buffer solutions for the work that would follow. The least squares regression equation is  $i_{pa} (\mu A) = 01434 + 0.1313V^{1/2}$ ; which indicates that the oxidation reaction of salicylic acid at a copper electrode is under diffusion-controlled process. The calculated standard deviation values confirm that both intraday and interday observations have a good degree of repeatability. When salicylic acid is combined with ascorbic acid and hydroquinone, there is a noticeable shift in the oxidation peak potential of the compound. The obtained recovery values highlight the suitability of the developed method based on the use of a copper wire electrode for the quantification of acetylsalicylic acid. All of the evaluated samples had RSD % values that were less than 2.02, proving the validity of the developed method.

## CONCLUSION

Despite the large number of analytical methods for the determination of ASA mentioned in the literature, the developed method, which is based on using inexpensive copper wire electrode without further modification in basic media for the quantitative analysis of ASA as SA, is a fast and expensive method that is suitable for routine quality control analysis in the pharmaceutical industry. The reported expanded dynamic range of salicylic acid, which ranges from 0.05mM to 15mM and

the achieved detection limit of 14.6 $\mu$ M support the usability of the voltammetric approach for acetylsalicylic acid measurement in the pharmaceutical industry. The precision of the developed method was found to be good for drug samples with an RSD of 2.2%.

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