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VALIDATION AND DETERMINATION OF ASCORBIC ACID IN MULTIVITAMIN TABLETS BY DIFFERENTIAL PULSE ANODIC STRIPPING VOLTAMMETRIC TECHNIQUE AT A BARE GLASSY CARBON ELECTRODE

(Validasi dan Penentuan Asid Askorbik dalam Tablet Multivitamin Menggunakan Teknik Voltammetrik Perlucutan Anodik Denyutan Pembezaan pada Elektrod Karbon Berkaca)

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Abstract

Growth of multivitamin tablet production increases curiosity among the researchers whether ascorbic acid (AA) content is in accordance with the standards or not. The differential pulse anodic stripping voltammetry (DPASV) technique using bare glassy carbon electrode and phosphate buffer at pH 4.2 has been proposed to analyse the ascorbic acid content. The experimental voltammetric parameters were optimized to obtain a maximum response with analytical validation of the technique. The optimum instrumental conditions for electroanalytical determination of AA by the proposed DPASV technique were initial potential = 0 V, final potential = 0.7 V, accumulation time = 60 s, scan rate = 0.125 V/s, accumulation potential = 0 V and pulse amplitude = 0.150 V. The curve was linear from 5 mg L^{-1} to 300 mg L^{-1} ($R^2 = 0.9999$) with detection limit of 0.25 mg L^{-1}. The precisions in terms of relative standard deviation (RSD) were 1.3%, 0.5% and 0.06%. The recoveries for AA content in the two multivitamin tablets were 98% and 102%, respectively. It can be concluded that the proposed technique is precise, accurate, rugged, low cost, fast and has the potential to be an alternative method for routine analysis of AA in other pharmaceutical products in future.

Keywords: ascorbic acid, glassy carbon electrode, voltammetry, multivitamin

Abstrak

Pertambahan penghasilan multivitamin dalam bentuk tablet telah meningkatkan rasa ingin tahu para penyelidik samada kandungan asid askorbik (AA) memenuhi piawaian atau tidak. Teknik perlucutan anodik denyutan pembezaan yang menggunakan elektrod karbon berkaca tanpa pengubahsuaian dan larutan penimbal fosfat (pH 4.2) telah dicadangkan untuk menganalisa kandungan asid askorbik. Parameter-parameter eksperimen voltammetrik dioptimakan untuk mendapatkan tindakbalas maksima diikuti dengan validasi atau pengesahan teknik voltammetrik. Keadaan instrumentasi optima untuk penentuan AA dengan menggunakan teknik DPASV yang dicadangkan adalah keupayaan awal = 0 V, keupayaan akhir = 0.70 V, masa penjerapan = 60 s, kadar imbasan = 0.125 V/s, keupayaan penjerapan = 0 V dan amplitud denyut = 0.15 V. Keluk penentukuran adalah lurus daripada 5 mg L^{-1} to 300 mg L^{-1} ($R^2 = 0.9999$) dengan had pengesanan 0.25 mg L^{-1}. Kejituan dalam bentuk sisihan piawai relatif adalah 1.3%, 0.5% and 0.06%. Perolehan semula peratusan kandungan AA di dalam dua tablet multivitamin adalah 98% dan 102%. Kesimpulannya, teknik yang dicadangkan adalah jitu, tepat, tahan lasak, melibatkan kos yang rendah, cepat dan berpotensi untuk menjadi satu kaedah alternatif untuk menganalisa AA dalam produk pharmaseutikal yang lain pada masa akan datang.

Kata kunci: asid askorbik, electrod karbon berkaca, voltammetri, multivitamin

Introduction

Vitamins are one of the major nutrients that play very important roles in the body. The vitamins involved in the processes of normal metabolism, cell regulation and they are necessary for growth and development. There are thirteen vitamins that are recognized contributing in human nutrition [1]. These vitamins can be divided into fat-soluble vitamins and water-soluble vitamins. Vitamin A, D, E and K are fat-soluble vitamins. Meanwhile, ascorbic acid (AA) and B-complex are water-soluble vitamins [2]. The water-soluble vitamins dissolve easily in water and are readily excreted from the body via urine [3].

The AA in food was discovered in the twentieth century in 1907 by Holst and Frolich as a solution for scurvy. During that year, the disease had been reported to be 'ship beriberi'. In order to avoid this disease, an experiment was done on guinea pigs by feeding them with fresh apples, fresh potatoes, fresh cabbage or fresh lemon juices which is high in the AA. The guinea pigs were also fed with a simple diet like oat, barley and wheat. The results indicated that deficiency of AA caused the scurvy [4]. The AA is also known as vitamin C, L-ascorbic and 2,3-didehydro-L-threohexono-1,4-lactone as well as 3-keto-L-gulofuranolactone. It has a chemical formula of $C_6H_8O_6$ and molecular weight of 176 $gmol^{-1}$ while its chemical structural is shown in Figure 1. The AA is important for collagen production, a protein which gives structure to bones, cartilages, muscles and blood vessels [5] as well as an antioxidant and free radical scavenger [6]. The AA also helps in iron absorption and maintains capillaries, bones and teeth [7]. The main natural sources of AA are various fruits and vegetables especially kiwi, mangoes, papayas, lettuce, tomatoes, peppers, strawberries, cantaloupe and broccolis [8].

It is known that humans cannot synthesize AA. Therefore, AA must be obtained by body through diet [9]. Pharmaceutical products such as multivitamins have become one of the sources of AA to meet requirement of daily dietary intake instead of fresh fruits and vegetables [10]. Unfortunately, the AA content in pharmaceutical products tends to be lost during processing, storing and packaging since it is highly sensitive to light, heat, temperature and oxygen [11]. Hence, it is very important to have a simple, very sensitive, precise, accurate, rugged, low cost and fast method for analysing AA even at a very low-level content.

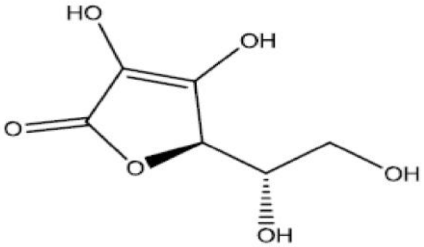

Figure 1. Chemical structure of ascorbic acid

Various analytical techniques have been applied for the AA determination. There are titrimetric method with an oxidant solution such as dichlorophenol (DCPIP) [12], potassium iodide or bromate [13], chromatographic method, particularly high performance liquid chromatography (HPLC) [11, 14, 15]**,** spectrometric method [3, 16, 17], capillary electrophoresis method [18, 19] and fluorimetry [20]. However, HPLC methods use expensive equipment, require a long time of sample pre–treatment, use toxic organic solvent as mobile phase and various harmful reagents [21]. In titrimetric method, the difficulties are encountered with titrants and interferences often occur with coloured samples which lead to lack of specificity [6]. Meanwhile, in direct spectrophotometry, there is a matrix effect in ultraviolet (UV) region since many organic compounds in samples may exhibit UV absorbance during measurement.

Voltammetry techniques seem to have high potential for an alternative analytical method as they are very powerful and versatile tool due to their simplicity, fastness, low waste emission, low cost of chemicals and instrumentation. They have comparable sensitivity to more expensive techniques and abundance direct individual or simultaneously analysis of analyte without any or minimal sample pre-treatment or extraction [22]. These techniques are less sensitive toward the matrix effects than the other analytical techniques. Electroanalytical techniques have been applied for qualitative and quantitative analysis of a wide range of drug compounds [23].

Square-wave voltammetric technique has been used to determine AA based on its oxidation at a zeolite modified carbon paste electrode as a working electrode [24]. Cyclic and differential pulse voltammetric techniques were also used for electrochemical behaviour investigation and determination of AA at a modified carbon paste electrode with 2,7-bis (ferrocenylethynyl) fluoren-9-one [25]. Carbon nanotube paste electrode modified with 2,2-[1,2-ethanediylbis (nitriloethylidine)]-bis-hydroquinone has been used for electrochemical behaviour investigation and determination of AA using cyclic and differential pulse voltammetric techniques [26]. A multi-walled carbon nanotubes-tetradecyltrimethylammonium bromide film coated graphite electrode was used to investigate the electro-oxidation of AA by applying cyclic, differential pulse voltammetric and square-wave voltammetric techniques [27]. Simultaneous determination of AA and dopamine was carried out by differential pulse voltammetric technique at a boron doped diamond electrode [28] and gold nanoparticles film electrode [29]. The simultaneous determination of AA and acetaminophen has been conducted by differential pulse voltammetric technique at a boron doped diamond electrode using sodium sulphate as the supporting electrolyte [30].

The purpose of this study is to develop and validate a differential pulse anodic stripping voltammetric (DPASV) technique using bare glassy carbon electrode as a working electrode and phosphate buffer solution (pH 4.2) as a supporting electrolyte for quantitative analysis of AA in multivitamin tablets without prior sample preparation.

Materials and Methods

Materials

All chemicals used in this study were of analytical grade reagent and all solutions were prepared in deionized water. The AA standard (MW = 176 g mol^{-1}) was obtained from Sigma Aldrich, UK. For the preparation of 1000 mg L^{-1} AA stock solution, 100 mg of the AA was dissolved in 100 mL volumetric flask. The standard working solution series were prepared by the appropriate dilution of the stock solution. All solutions were protected from light and used within 24 hours to avoid decomposition. Phosphate buffer solution (PBS) was prepared by adding and dissolving 2.70 mL of ortho phosphoric acid, 27.218 g of potassium dihydrogen phosphate, 71.630 g disodium hydrogen phosphate in the 1000 mL of volumetric flask. Sodium hydroxide with the concentration of 0.1 M was used to adjust the pH of the PBS solution to the pH 4.2.

Instrumentation

The voltammetric experiments were carried out using Autolab (Metrohm, Switzerland) that consisted of a glassy carbon electrode (GCE) as the working electrode (WE), a platinum wire as the auxiliary electrode (AE) and an Ag/AgCl (3M KCl) as the reference electrode (RE). The GCE was polished with polishing alumina on an alumina pad and then rinsed with deionized water. The Autolab was connected to a computer, installed with NOVA 1.1 for data processing. The pH meter (Hanna Instruments, UK) was employed for all pH measurements.

Voltammetric measurement: Differential pulse anodic stripping voltammetry (DPASV)

AA standard working solution was spiked into the PBS solution at pH 4.2 to give the final concentration of 10 mg L^{-1}. The initial operational instrumental parameters applied were initial potential (E_i) = 0 V, final potential (E_f) = 0.7 V, accumulation time (t_{acc}) = 10 s, scan rate (v) = 0.05 V/s, accumulation potential (E_{acc}) = 0 V and pulse amplitude = 0.075 V. These instrumental parameters for voltammetric measurements were optimized to increase the response of the proposed DPASV technique.

An appropriate linear range with acceptable correlation coefficient (R^2), limit of detection (LOD), limit of quantification (LOQ), precision, accuracy, ruggedness and recovery of AA standard in the pharmaceutical samples were analysed in order to verify the suitability of the proposed DPASV technique for AA analysis as proposed by Miranda et al. [31]. The LOD was determined by additional lower concentration of the AA standard solution until obtaining a response that was significantly different from PBS solution at pH 4.2. The LOQ were calculated by the equations; LOD = 3 SD/m and the value of the LOQ was 3.333 times the value of the obtained LOD. The AA standard solution at the concentration of 5, 50 and 150 mg L^{-1} was applied for intra-day and inter-day precision, ruggedness and robustness with five replicates (n=5). The ruggedness of the proposed DPASV technique was investigated using the same instrument (Autolab) but had been conducted by two different analysts under the same optimum parameters. Statistical *F*-test was carried out for the ruggedness and robustness.

Collection and preservation of multivitamin tablets

Two different brands of multivitamin tablets with different labelled content of AA were obtained from a pharmacy in Jengka, Pahang. The multivitamin tablets of each brand were ground to a fine powder and dissolved in 200 mL of deionized water. Then, the samples were transferred to a covered scotch bottle to avoid degradation.

Recovery studies of AA standard in multivitamin tablets

The recovery of AA standard solution in the multivitamin tablet was determined by spiking 0.5 mL of the sample into the measuring cell containing PBS solution at pH 4.2. This study was carried out with three replicates (n = 3). Recovered concentrations of the spiked AA standard solution in the samples were calculated using the regression equation from a calibration curve from the following formula in equation 1 [32];

$$C_{\text{sample}} = \frac{C_{\text{means solution}} \times V_{\text{total}}}{V_{\text{sample}}} \qquad (1)$$

where, $C_{\text{means solution}}$ is concentration in the measuring solution (mg L^{-1}), V_{total} is total volume of the measuring solution (L), V_{sample} is volume of sample in the measuring cell (L) and C_{sample} is concentration in the sample (mg L^{-1}).

Results and Discussion

DPSAV of AA

DPSAV offers a well-defined and sharp peak even at lower concentration of AA [5]. It is very important to optimize all the parameters that may influence the measurements in order to obtain the optimum response [33]. The effects of scan rate (v), accumulation time (t_{acc}), accumulation potential (E_{acc}) and pulse amplitude on the I_p of 10 mg L^{-1} AA standard were studied in the PBS solution at pH 4.2.

The effect of accumulation time (t_{acc})

An accumulation time (t_{acc}) is a period of time given for AA to accumulate or adsorb onto a glassy carbon electrode before being analysed further. The t_{acc} is strongly affected by the peak response and contributed to the high peak in electroanalytical measurements [34]. The influence of t_{acc} on the peak response of AA in PBS solution at pH 4.2 has been studied over the range between 10 to 80 s. The I_p has increased starting from 10 s to 60 s. The t_{acc} of 60 s was considered as the optimum t_{acc} as the highest I_p has been obtained, which was 426 nA, as shown in Figure 2.

The increase of the I_p of AA with t_{acc} was contributed by the accumulation of AA at the electrode surface in large amount since longer time has been given for the accumulation to occur [35]. Besides, the higher response of measurement can be achieved with longer of t_{acc}. After the t_{acc} of 60 s, the I_p has decreased probably due to saturation of the accumulated AA at the working electrode surface [36].

The effect of scan rate (v)

The relationships between I_p of AA and various v such as 25, 50, 75, 100, 125 and 150 mV/s were observed using the initial parameters. The maximum current obtained was 469 nA at E_p of 0.39978 V with v of 0.125 V/s in PBS solution at pH 4.2

The effect of accumulation potential (E_{acc})

Accumulation potential (E_{acc}) was the potential for AA to be accumulated at the surface of a mercury electrode, whereas an optimum E_{acc} was the most appropriate potential for the accumulation process to take place [34]. Figure 3 shows the maximum response was observed at E_{acc} of 0 mV with I_p 469 nA and E_p of 0.39978 V. It indicated that the accumulation of AA at the electrode surface effectively occurred at 0 mV.

The effect of pulse amplitude

According to De Lima et al. [37], pulse amplitude is one of the factors that affects the sensitivity of voltammetric measurements. The I_p and E_p have sharply increased from 0.075 V to 0.15 V and slowly decreased after 0.15 V, as shown in Figure 4. The pulse amplitude of 0.15 V was noted as optimum condition for analysis due the highest I_p observed which was 857 nA and E_p of 0.3598 V in PBS solution at pH 4.2.

Validation of the developed method: Linearity, limit of detection (LOD) and limit of quantification (LOQ)

The capability of the proposed DPASV technique as an analytical method for determination of AA was studied by evaluating the obtained I_p as the function of concentration under the optimized operational and instrumental parameters. The constructed calibration graph from 5 to 300 mg L^{-1} was represented by the linear equation of I_p (nA) = 109.79x – 224.01 with 0.9999 of correlation coefficient (R^2), as shown in Figure 5.The observed LOD for the standard solution was 0.25 mg L^{-1} and the LOQ was found to be 0.83 mg L^{-1}.

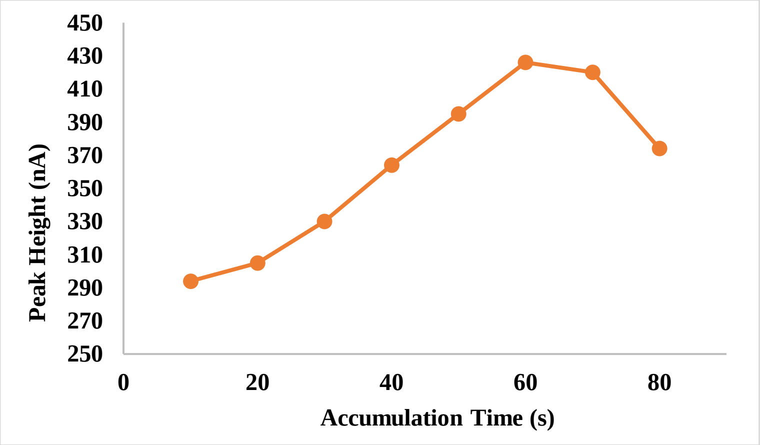

Figure 2. Plot of I_p against accumulation time (t_{acc}) of AA in phosphate buffer solution pH 4.2

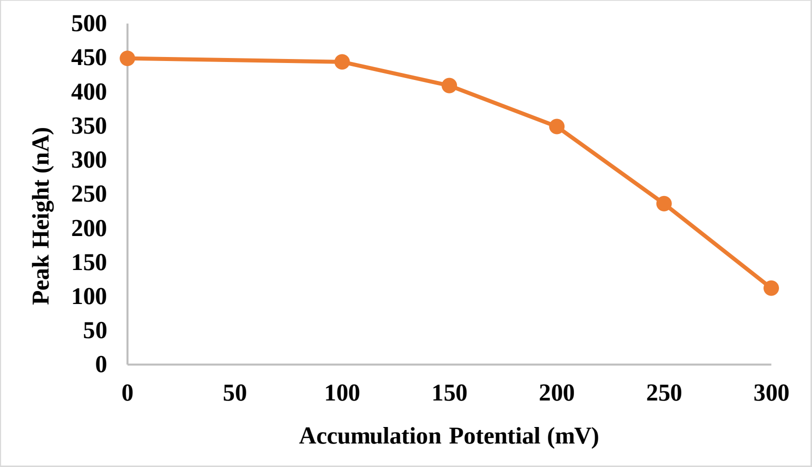

Figure 3. Plot of I_p against accumulation potential (E_{acc}) of AA in phosphate buffer solution pH 4.2

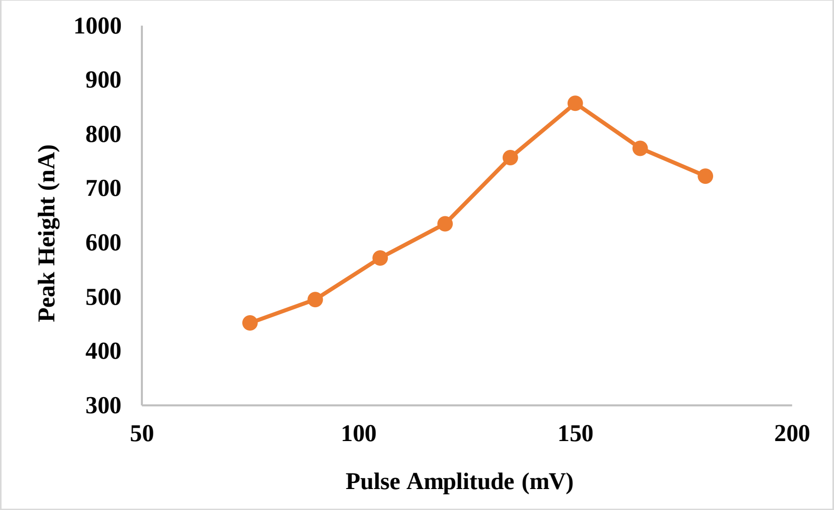

Figure 4. Plot of I_p against pulse amplitude in phosphate buffer solution pH 4.2

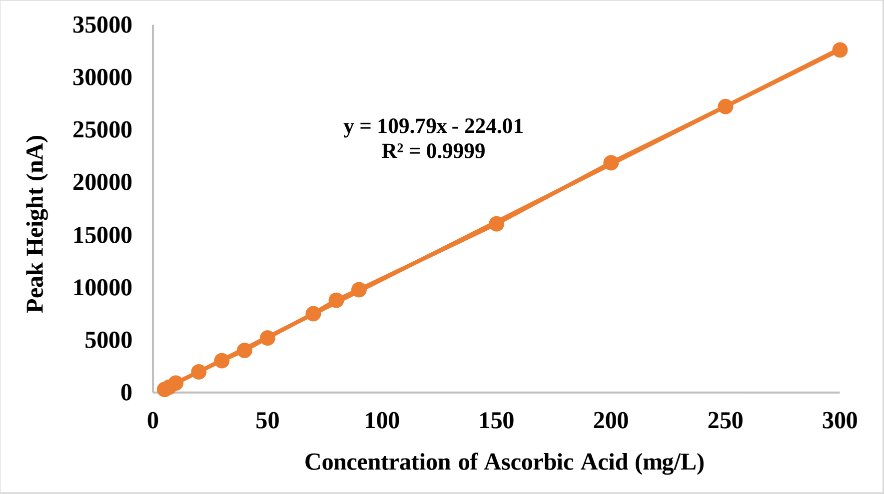

Figure 5. Linear curve of I_p against concentration of ascorbic acid in phosphate buffer solution pH 4.2. Instrument parameters were E_i = +0 V, E_f = 0.7 V, t_{acc} = 60 s, *v* = 0.125 V/s, E_{acc} = 0 V and pulse amplitude = 0.15 V

Precision

The precision of the proposed DPASV technique for AA analysis was determined in three replicates (n=3) at the concentrations of 5 mg L^{-1}, 50 mg L^{-1} and 150 mg L^{-1}. The RSD values obtained were 1.3%, 0.5% and 0.06% for respective concentrations. The RSD values found to be less 5% indicating that the measurements were precise and confidence [38].

Accuracy

The accuracy of the developed technique was tested by spiking three known different concentrations of AA which were 5 mg L^{-1}, 50 mg L^{-1} and 150 mg L^{-1} into a voltammetric cell containing PBS solution at pH 4.2. These spiked AA standard solutions were measured in three replicates (n=3) and the discovered amounts of the spiked solutions in the cell were calculated using the equation of I_p (nA) = 109.79x – 224.01, where x is the found concentrations of AA in the voltammetric cell. The satisfactory recoveries of 93.08 %, 98.66 % and 99.00 % were respectively achieved for the spiked concentrations of 5 mg L^{-1}, 50 mg L^{-1} and 150 mg L^{-1}.

Ruggedness

The RSD values ranged from 0.07 % to 2.93 % for the first and second analyst, respectively for the measurements of 5 mg L^{-1}, 50 mg L^{-1} and 150 mg L^{-1} AA using the same instrument [39]. From the two-tailed *F* test, there were no significant differences between the obtained variances for AA when the measurements were performed by two different analysts with the same instrument at the 5 % significance level. Hence, the results indicated that the developed technique was considered rugged.

Determination of AA in multivitamin tablets

To evaluate the application to a real sample analysis, the developed DPASV technique was used to analyse AA in multivitamin tablets. The multivitamin tablets were analysed by the developed technique under optimum parameters without any sample pre-treatment. Table 1 shows the content of AA in the multivitamin samples.

Assay results for the determination of the AA in the multivitamin tablets are shown in Table 2 by comparing the actual AA content with the labelled AA content in terms of mg/tablet [32]. The samples were analysed under the optimum instrumental parameters. The recoveries achieved for AA content in Sample A and B were 98 % and 102 %, respectively. These satisfactory recoveries indicated that the matrix did not affect the measurement of the AA in the multivitamin tablets by the proposed DPASV technique.

Table 1. Ascorbic acid content in the multivitamin tablet were analysed by the proposed DPASV technique in phosphate buffer solution at pH 4.2 (n = 3)

Sample	**I_p (x 10^{-7} A) ± SD (RSD)**	**Concentration of Ascorbic Acid (mg/L)**
A	4.40 ± 0.15 (3.40%)	490
B	8.19 ± 0.12 (1.46%)	769

Table 2. Assay results for the determination of the AA in multivitamin tablets

Sample	**Labelled Content (mg/tablet)**	**Actual Content (mg/tablet)**	**Recovery (%)**
A	100	98	98
B	150	153	102

Conclusion

The proposed DPASV technique had been successfully applied to determine the AA in multivitamin tablets. The present method had an advantage that a very simple sample pre-treatment was required. It was also found to be practically rapid, convenient, sensitive, accurate, precise, rugged and low in cost. Therefore, it could be an excellent alternative method for the routine determination of AA in the multivitamin tablets.

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