

Cathodic Stripping Voltammetric Determination of Dimenhydrinate
تعيين المركب الدوائي dimenhydrinate بطريقة الانتزاع المهبطي الفولتمي على قطرة
زئبق

Raqi Shubietah* & Ali Abu Zuhri

راقى شبيطة، وعلي أبو زهري

*Faculty of Medicine & Health Sciences, An-Najah National University,
Nablus, Palestine

*Corresponding Author, E-mail: raqi@najah.edu

Received: (1/12/2013), Accepted: (17/9/2014)

Abstract

Dimenhydrinate (DMH) is a derivative of theophylline (diphenhydramine salt of 8-chloro theophylline). Both dimenhydrinate and theophylline are used as antihistamines in treatment of asthma, in addition to other important pharmaceutical uses. A three-electrode voltammetric system was used, with hanging mercury drop electrode (HMDE) as working electrode. A reduction peak of DMH at -0.2 to -0.3 V in acetate buffer, pH about 4.0 is obtained. The peak height is increased largely (tripled) in presence of Cu^{2+} , due to the formation of DMH-Cu (I) complex. The detection limit is as low as 5×10^{-9} M DMH. Application of the analysis of two drugs containing dimenhydrinate was carried out, where a coefficient of variation of about 3% was obtained.

Key words: dimenhydrinate, voltammetric analysis, stripping voltammetric determination

ملخص

استخدمت الطريقة المذكورة عند درجة حموضة $pH = 4$ في محلول منظم من الأسيتات مع حمض الخليك لتعيين تراكيز منخفضة من المادة الدوائية المذكورة وهي من البورينات وتشبه في تركيبها الثيوفيلين المستخدم في علاج الأزمة. وقد تم رسم النتائج في منحنى معياري

فكان تناسب التركيز طردياً مع قيمة التيار الكهربائي المقاس في المدى: $1 \times 10^{-8} \text{ M} - 2 \times 10^{-7} \text{ M}$. أما الحد الأدنى من التراكيز التي يمكن قياسها فكان $5 \times 10^{-9} \text{ M}$ ، وتعتبر الطريقة رخيصة ودقيقة النتائج (معدل الانحراف العياري 3%) كما أنها لا تلوث البيئة ولا تستخدم فيها كميات كبيرة من المواد والمذيبات. والكشف عن البورينات ومنها الدايمنهيدرينيت له أهمية في الرقابة الدوائية وكذلك يعتبر وجود بعض البورينات التي أثرت العمليات الحيوية على تركيبها مؤشراً على أمراض مثل السرطان. ووجود تراكيز منخفضة ($1 \times 10^{-7} \text{ M}$) من أيون النحاس الثنائي تزيد بدرجة كبيرة قد تصل إلى ثلاثة أضعاف من ارتفاع القمة أي التيار الكهربائي الناتج. وقد تم تطبيق طريقة التحليل المذكورة على أقراص دواء وكانت الطريقة ناجحة ودقيقة.

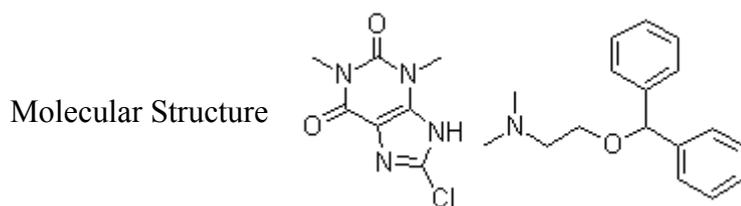
Introduction

Dimenhydrinate (DMH) is widely used for preventing subjective symptoms and gastric dysrhythmias associated with motion sickness, and for prevention of post-operative nausea and vomiting in female in-patients (Anquist, K., Panchanathan, S., Rowe, P., Peterson, R., et al, 1991, Weinstein, S., 1997 & Eberhart, L., Seeling, W., Bopp, T., Morin, A. et al, 1999). Modified urinary purine nucleosides are potentially strong indicators of cancer. Few papers were published about the analysis of the family of this drug (purines), which included spectroscopy (Delaye, F, Gaye, M. & Aaron, J, 1989, Vlassa, M., Filip, M., Pascalau, V., Coman, V., et al, 2009), high performance liquid chromatography (Kazoka, H., 2007, Reynal, S., & Broderick, G., 2009), fluorimetry (Katayama, M. & Taniguchi, H., 1989), GC-mass spectrometry (Verdugo, D, Cancilla, M, Ge, X, Gray, N, et al, 2001) and voltammetry (Deng, Q., Kauri, L., Qian, W., Dahlgren, G. & Kennedy, R, 2003).

Oliveira-Brett, A., Piedade, J, Silva, L & Diculescu, V, 2004, Shubietah, R. Abu Zuhri, A., & Fogg, A., 1994, Xiang, S., Yumei, C., & Hongyuan, C, 1993, Shubietah, R. Abu Zuhri, A., & Fogg, A., 1999). Cefoperazone in spiked human urine was determined with no matrix effect, using HMDE and Britton Robinson buffer pH 3-6 (Vu Dang, H., Dao, H., & Hong, P., 2013). Voltammetric assays of pharmaceuticals were reviewed by some authors (Gupta, V., Jain, R., Radhapyari, K., Jadon, N., Agarwal, S., 2011).

A single research (Shubietah, R. Abu Zuhri, A., & Fogg, A., 1999) was published about adsorptive stripping voltammetry of

dimenhydrinate, in addition to a study (Shubietah, R. Abu Zuhri, A., & Fogg, A., 1994) of theophylline, which has a close structure of DMH. Here in this research, the voltammetric analysis was done to construct two calibration curves of dimenhydrinate in absence of copper ions. The formation constant of copper-dimenhydrinate complex was calculated, and anodic stripping voltammetry was also studied. Cyclic voltammetry of DMH was demonstrated, and the mechanism of reduction was deduced to involve two electrons per molecule. Recent studies in voltammetric research have utilized the carbon nanotubes in the preparation of electrochemical biosensors (Agui, L., Yanez-Sedeno, P., & Pingarron, J.M., 2008), complexation with Al^{3+} at the hanging mercury drop electrode (HMDE) surface for the diagnosis of Parkinson's and Alzheimer's diseases through monitoring low concentrations of dopamine (Zhang, F., Zhang, M., Cheng, J., Yang, L., et al, 2007), and monitoring the effects of nano- Al_2O_3 on the enzyme 'lactate dehydrogenase', of which levels of concentration can indicate gastric cancer, breast cancer and lung damage (Yao, K., Huang, D., Xu, B., Wang, N., et al, 2010). In this paper, a stripping voltammetric study is focused on DMH, using a HMDE as a working electrode, in absence and in presence of enough concentration (about 10^{-6} M) of Cu (II).



Dimenhydrinate (DMH)

Molecular Formula $C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$

Methodology

voltammetric measurements were carried out in a 30 ml cell with HMDE as working electrode, Ag/AgCl as reference electrode and platinum wire as auxiliary electrode. Purging the sample solution with

nitrogen for 6 minutes was done to eliminate the dissolved oxygen from giving a reduction peak. During the accumulation time, the stirring was going on until only 10 seconds are left. Then, the stirring was switched off to give the solution a quiescent time before measurement is taken. Usually, the scanning was started from 0.0 V to -0.60 V, as the peak potential varies from -0.2 V to -0.3V. Measurements were carried on using the 663 stand, coupled to EG &G voltammeter, with differential-pulse cathodic stripping voltammetry as the technique. The blank is deaerated similar to the sample, and the voltammogram is recorded. For the detection limit determination, the accumulation was increased to 3 minutes in presence of 10^{-6} M of Cu(II). Doubly distilled water was used for all solutions, and all buffers were prepared from this water. All chemicals were of analytical grade, produced by Merck. The stock solution of DMH (10^{-3} M) was prepared and kept after analysis in the refrigerator, for 4-5 weeks.

Optimum parameters for the analysis of DMH

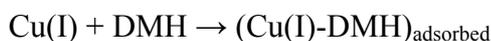
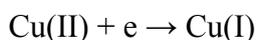
Acetate buffers of different pH values were used to search for optimum pH value for stripping voltammetry of DMH. The pH value of about 4 was chosen as optimum (see Table 1). The concentration of acetate buffer was also studied. No change of peak current was observed when 0.20 M acetate buffer was diluted, until concentration was 0.02 M. For those concentrations of buffer between 0.015M and 0.010 M, the peak current decreased by 50%. Adsorption at the hanging mercury drop electrode (HMDE) is less when pH gets higher than 4-4.2. A Britton Robinson buffer (BR) of pH=4.00 gave a less peak height than the acetate buffer of same pH (2.6 nA at -0.28 V). Optimum accumulation potential was 0.0 V, although accumulation at + 0.1 V gives similar peak currents. Better baseline start is obtained with 0.0 V accumulation than with + 0.1 V. DC-CSV for 1×10^{-6} M DMH shows linear dependence of peak current on the scan rate. This is a result of adsorption phenomenon at the surface of HMDE.

Table (1): Effect of pH of acetate buffers on the peaks of 1×10^{-6} M DMH, using HMDE and DP-CSV. Pulse amplitude=50mV, scan rate 5mVs^{-1} , accumulation time=60 sec, accumulation potential=0.0 V

| pH | Peak current(nA) | Peak potential(V) |
|------|------------------|-------------------|
| 3.70 | 2.5 | -0.17 |
| 4.00 | 3.0 | -0.20 |
| 4.30 | 2.8 | -0.22 |
| 4.70 | 2.4 | -0.24 |

Complexation of DMH with copper ions

A stable copper(I) complex with DMH is expected to form at the accumulation potential. Copper (II) complexes also form, but they are less stable:



Both the above two reactions occur at the surface of HMDE (see Fig 1). Copper (I) ions are more stable, being reduced from Cu (II) in the cathodic scanning. It is more difficult to oxidize Cu (0) to Cu (I) in the anodic scanning, thus cathodic peaks are noticeably greater than anodic peaks. DMH is released as a free ligand at the peak potential, where Cu (I) is reduced to Cu(0) also. Cu (II)- DMH complex is also formed at more positive potentials. The reduction of Cu(II)-DMH complex to Cu(I) and DMH occurs at about -0.15 V, but reduction of the Cu(I)-DMH complex to Cu(0) and released DMH occurs at about -0.3 V. The nature of this complexation was illustrated experimentally by exposing the HMDE with adsorbed DMH-Cu complex at its surface to air for 5 seconds during the equilibration 15 seconds time. This exposure caused oxygen to partially oxidize Cu (I)-DMH to Cu (II)-DMH complex as deduced from the change in peak currents.

When a fixed concentration($=10^{-6}$ M) of Cu(II) was used, to which successive additions of DMH were made, an estimation of the number of ligands (n) in the complex formula, Cu(DMH)_n could be made. If

C =molar concentration of ligand for a specific solution, i =peak current, i_m = maximum peak current when complexation is judged complete and β = stability constant of the complex, then (Jin,W., & Li, X., 1990):

$$1/i = 1/i_m + 1/(\beta i_m C^n)$$

By substituting different values of n , a straight line of this last equation is obtained only for $n=2$ (mole ratio of DMH: Cu). So, the complex composition is $\text{Cu}(\text{DMH})_2$. The value of β was found to be 2.8×10^{12}

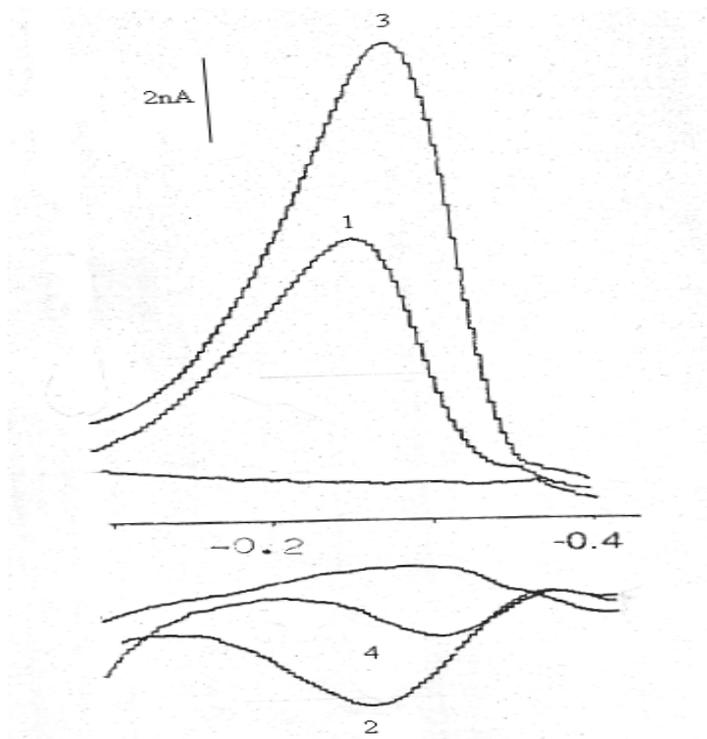


Fig (1): DP-CSV(cathodic stripping voltammetry): peak 1, and DP-ASV(anodic stripping voltammetry):peak 2, of 5×10^{-7} M DMH.

Peak 3=peak 1 + 1×10^{-7} M Cu(II), peak 4=peak 2 + 1×10^{-7} M Cu(II)

$t_{acc}=2$ minutes, at 0 V for CSV, and at -0.4 V for ASV

scan is being done from the accumulation potential to more negative potentials-CSV- or to more positive potentials-ASV-.Acetate buffer pH=4.00, scan rate = 5 mVs⁻¹, pulse amplitude = 50 mV.

The IR spectrum of pure DMH was compared with that of its copper complex, and a weakening of the NH bands at about 3300 cm⁻¹ was observed, suggesting a removal of the hydrogen atom from N-7 of the imidazole moiety of DMH, as a result of complexation.

Fig 2 shows the cathodic peaks only for pure DMH and its Cu(I) complex. Addition of Cu (II) to a fixed concentration of DMH increases the reduction current, but the current increments are nonlinear, perhaps due to saturation of the small size HMDE. The low currents produced by DMH in the absence of Cu (II) are suggested to be tensammetric, ie adsorption/desorption phenomenon. In presence of Cu (I) in the cathodic scan, a larger faradaic current is produced. Cu (I) is reduced to Cu (0) at the desorption potential of DMH.

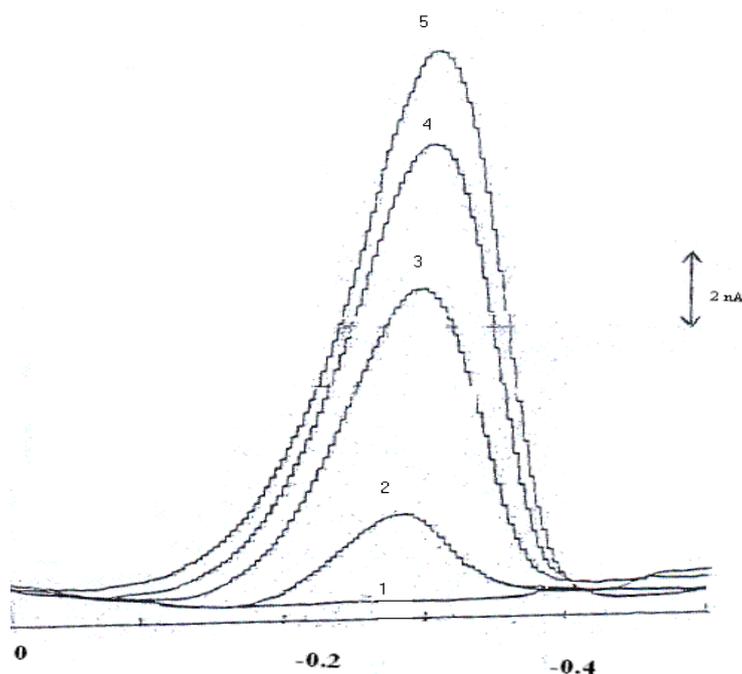


Fig (2): DP-AdCSV voltammograms of:

- 1) blank = acetate buffer, pH=4.0
- 2) blank + 1.0×10^{-6} M DMH
- 3) 1.0×10^{-6} M DMH + 1.2×10^{-7} M Cu^{2+}
- 4) 1.0×10^{-6} M DMH + 2×10^{-7} M Cu^{2+}
- 5) 1.0×10^{-6} M DMH + 3×10^{-7} M Cu^{2+}

$E_{\text{acc}}=0.0\text{V}$, $t_{\text{acc}}=1$ minute, scanned from 0.0 to -0.50V at 5 mVs⁻¹ and 50 mV pulse amplitude.

Polarographic results of DMH alone and in presence of Cu(II) were not encouraging, as low currents were produced and broad peaks were obtained. Only stripping analysis of the voltammetric work, particularly in the cathodic scan is valuable for DMH. The anodic scan, although of

lower currents, has the advantage of extending the linear range of concentrations.

Fig (3) shows cyclic voltammograms of DMH alone and its copper complex. As cathodic current/anodic current > 1, then a quasi-reversible, but not reversible, electrode reaction is deduced. For a reversible reduction of an electrode process, with number of electrons transferred= n (Baiser, M., & Lund, H.,1983):

$$E_{\text{peak (anodic)}} - E_{\text{peak (cathodic)}} = 0.057/n \quad \text{at } 25^{\circ}\text{C}$$

Provided the switching potential is at least $(100/n)$ mV past the cathodic peak potential. In our results, the difference between the two peak potentials is about 28mV, suggesting a two-electron process of reduction.

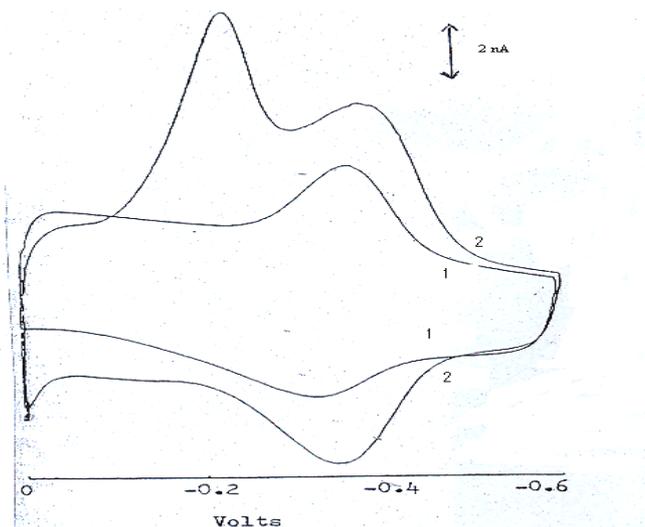
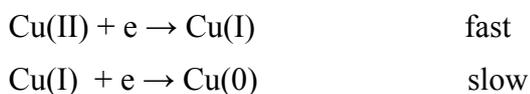


Fig (3): Cyclic voltammograms of
 (1) 1.0×10^{-5} M DMH
 (2) 1.0×10^{-5} M DMH + 1.0×10^{-6} M Cu^{2+}

Accumulation at 0.0 V for 2 minutes, scanning from 0.0 to -0.6 V

The effect of increasing the concentration of DMH (up to 1.5×10^{-6} M) on the anodic peak current is shown in Fig 4. This high top linear concentration is not possible when using high cathodic currents. However, cathodic peaks offer higher sensitivity and better linearity, for more dilute solutions.

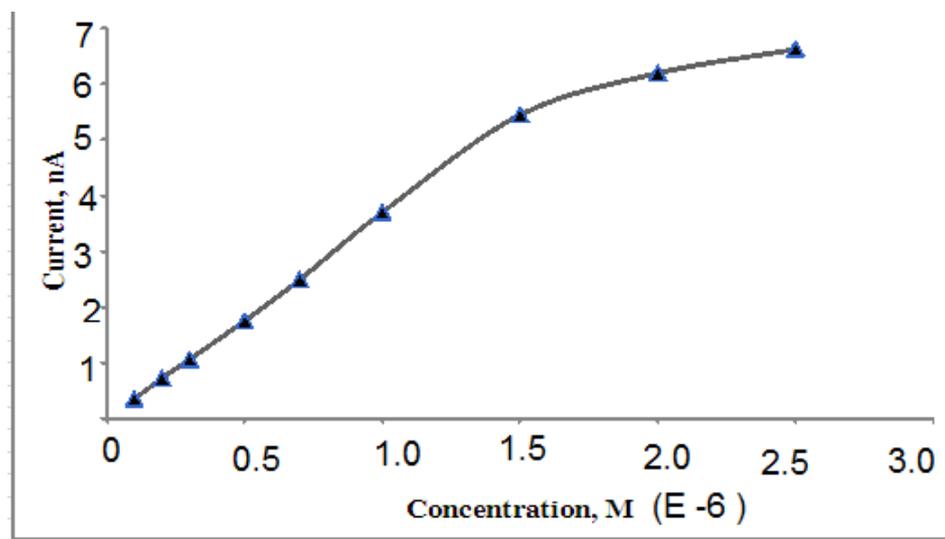


Fig (4): DP-ASV (anodic stripping voltammetry) of DMH in acetate buffer pH 4.0, $t_{acc}=5$ minutes, peak potential ranges from -0.25 V to -0.30 V.

Interference effects on the DMH peak

The peak current of 1×10^{-6} M DMH was studied with few cations and anions.

It was found that, the presence of Perchlorate, nitrate and sulfate anions have a slight decrease effect (about 15%) on the mentioned peak current. Chloride causes about 50% decrease at 0.02 M Cl^- , and 90% decrease in presence of 0.10 M Cl^- . EDTA and citric acid cause large decrease in this peak current at 0.02 M level, but the peak totally disappears when 0.05 M of these two interferents is used. Triton X-100

as a surface-active material causes about 70% decrease at 0.05 M level, but the peak disappears at concentrations = 0.1M.

For metal ions, Zn(II) and Cd(II) increase the mentioned peak current by about 30% at concentrations 10^{-6} to 10^{-5} M. Cu(II) increases the peak current by about 100% at 10^{-6} M level, and 150% at 10^{-5} M level. Metal ions Pb(II), Co(II), Ni(II), Au(III), La(III), and Ag(I) have negligible enhancements on the peak current of 1×10^{-6} M DMH.

Determination of DMH in dosage forms

The slope of the calibration curve (Fig 5) is 4.93×10^7 nA/M and the detection limit under these conditions is around 1×10^{-8} M DMH. The linearity was observed from the detection limit to about 2×10^{-7} M. Coefficient of variation (C.V.) (6 determinations) at 1.5×10^{-7} M level was 3%.

Two tablet formulations containing only dimenhydrinate were analysed, referring to this calibration curve. Dramamine tablets/England gave an assay of 99.1% of the claimed amount (C.V. about 2.8%), and dizinil tablets/United Arab Emirates gave an assay of 97.5% of the claimed amount (C.V. 3.3%).

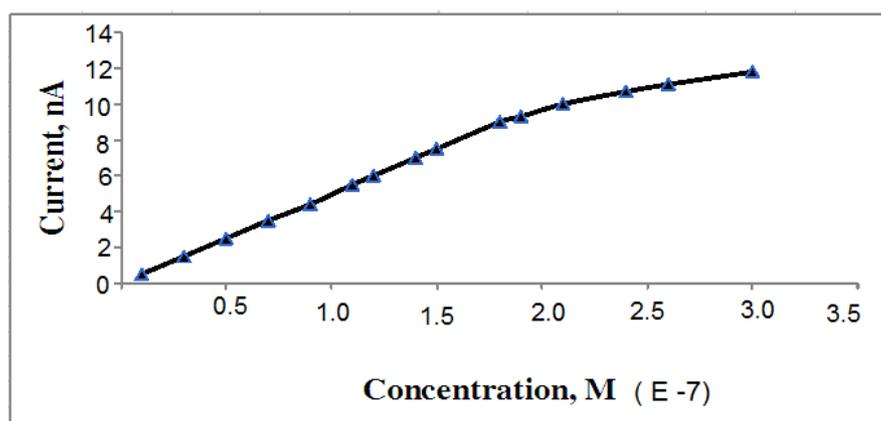


Fig (5): DP-CSV(cathodic stripping voltammetry)calibration curve of DMH, after accumulation of 5 minutes at the HMDE in acetate buffer pH 4.0, pulse amplitude 100 mV and scan rate 10 mVs^{-1}

Conclusion

A linear dependence of peak current on the concentration of dimenhydrinate is observed in a limited range 1×10^{-8} to 2×10^{-7} M DMH. This range offers good sensitivity and trace amounts of the drug can be detected. Routine analysis using this method is possible, as it is cheap and not harmful to the environment. The obtained calibration curve is stable and need not be repeated each day the analysis is run. Highly purified water should be used, to avoid possible interferences.

References

- Agui, L. Yanez-Sedeno, P. & Pingarron, J.M. (2008). *Role of carbon nanotubes in electroanalytical chemistry: A review*. *Anal.Chim.Acta*, 622(1-2), 11.
- Anquist, K. Panchanathan, S. Rowe, P. Peterson, R. & Sirnick, A. (1991). *Diagnostic delay after dimenhydrinate use in vomiting children*. *CMAJ*, 145(8), 965
- Baiser, M. & Lund, H. (1983). *Electrode kinetics and electrocatalysis in organic electrochemistry*. *Organic Electrochemistry*, Marcel Dekker, Inc., 2nd edition, pp83-84.
- Delaye, F. Gaye, M. & Aaron, J (1989). *Evaluation of computer-assisted second derivative ultraviolet spectrophotometry for analysis of binary mixtures*. *Anal.Chim. Acta*, 223, 395.
- Deng, Q. Kauri, L. Qian, W. Dahlgren, G. & Kennedy, R. (2003). *Microscale determination of purines in tissue samples by capillary liquid chromatography with electrochemical detection*. *Analyst*, 128,1013
- Eberhart, L. Seeling, W. Bopp, T. Morin, A. & Georgieff, M. (1999). *Dimenhydrinate for prevention of post-operative nausea and vomiting in female in-patients*. *European Journal of Anaesthesiology*, 16 (5), 284

- Gupta, V. Jain, R. Radhapyari, K. Jadon, N. Agarwal, S. (2011). *Voltammetric techniques for the assays of pharmaceuticals-A review*. Analytical Biochemistry, 408 (2), 179
- Jin, W. & Li, X. (1990). *1.5th – and 2.5th – order derivative adsorption voltammetry of the Cobalt (II)-2-(5'- bromo-2'-pyridylazo) - diethylaminophenol system*. Anal. Chim. Acta, 236, 453
- Katayama, M. & Taniguchi, H. (1989). *Fluorometric reactions of purines and determination of caffeine*. Talanta, 36, 1171
- Kazoka, H. (2007). *HPLC separation of some purine and pyrimidine derivatives on Chromolith Performance Si monolithic column*. Journal of Biomedical and Biophysical Methods, 70(1), 15
- Oliveira-Brett, A. Piedade, J. Silva, L. & Diculescu, V. (2004). *Voltammetric determination of all DNA nucleotides*. Analytical Biochemistry, 332, 321.
- Reynal, S. & Broderick, G. (2009). *A new HPLC assay for quantifying microbial flow*. Journal of Dairy Science, 92(3), 1178
- Shubietah, R. Abu Zuhri, A. & Fogg, A. (1999). *Adsorptive stripping voltammetric determination of dimenhydrinate at a hanging mercury drop electrode*. Mikrochim. Acta, 130, 165.
- Shubietah, R. Abu Zuhri, A. & Fogg, A. (1999). *Adsorptive stripping voltammetric determination of dimenhydrinate at a hanging mercury drop electrode*. Mikrochim. Acta, 130, 165.
- Shubietah, R. Abu Zuhri, A. & Fogg, A. (1994). *Adsorptive cathodic stripping voltammetric determination of theophylline at a hanging mercury drop electrode*. Analyst, 119, 1967.
- Shubietah, R. Abu Zuhri, A. & Fogg, A. (1994). *Determination of nanomolar levels of guanine by differential-pulse adsorptive cathodic stripping voltammetry of its copper (II) complex*. Fresenius' Journal of Analytical Chemistry, 348(11), 754.

- Verdugo, D. Cancilla, M. Ge, X. Gray, N. Chang, Y. Schultz, P. Bertozzi, C. (2001). *Discovery of estrogen sulfotransferase inhibitors from a purine library screen*. J. Med. Chem., 44 (17), 2683.
- Vlassa, M. Filip, M. Pascalau, V. Coman, V. & Dragomir, C. (2009). *Determination of purine derivatives in bovine urine using rapid chromatographic techniques*. Archiva Zootechnica, 12(4), 59.
- Vu Dang, H. Dao, H. & Hong, P. (2013). *Determination of cefoperazone in spiked human urine*. Science.gov,1(1)
- Weinstein, S. (1997). *Comparison of amerazine and Dramamine in preventing symptoms of motion sickness*. Aviat Space Environ Med, 68(10), 890.
- Xiang, S. Yumei, C. & Hongyuan, C. (1993). *Electrochemical behavior of guanine and its determination by differential pulse adsorption stripping voltammetry*. Microchem. J., 47, 287
- Yao, K. Huang, D. Xu, B. Wang, N. Wang, Y. & Bi, S. (2010). *A sensitive electrochemical approach for monitoring the effects of nano- Al_2O_3 on LDH activity by differential pulse voltammetry*. Analyst 135(1), 116.
- Zhang, F. Zhang, M. Cheng, J. Yang, L. Ji, M. & Bi, S.(2007). *Direct voltammetric specific recognition of dopamine using Al (III)- DA complexes at a hanging mercury drop electrode*. Ana. Scli., 23(11), 1325.