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Original article

THE DETERMINATION OF BUPROPION HYDROCHLORIDE IN PHARMACEUTICAL DOSAGE FORMS BY ORIGINAL UV- AND SECOND DERIVATIVE UV SPECTROPHOTOMETRY, POTENTIOMETRIC AND CONDUCTOMETRIC METHODS

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Abstract

Spectrophotometric, potentiometric and conductometric methods are developed for the determination of bupropion hydrochloride (BUP) in pharmaceutical tablets. For the first method, original UV-spectrophotometry, 252 nm was determined as the optimum wavelength and used for the determinations. For the other method, second derivative UV spectrophotometry, the absorbances were measured at 217.4 and 221.8 nm and the distance between these extremum values was determined according to peak to peak method. Two spectrophotometric methods were validated over the concentration range of 5.72 – 20.03 µg/mL. The limit of detection and limit of quantitation values of original UV-spectrophotometry were 0.75 µg/mL and 2.28 µg/mL. Also, these parameters were determined as 0.23 µg/mL and 0.68 µg/mL respectively, for the second derivative UV spectrophotometry. Developed methods were fully validated and the applicability of the methods for the determination of BUP in pharmaceuticals were demonstrated. Also, simple potentiometric and conductometric methods were developed and the applicability of these methods were demonstrated. The results of four analytical methods were compared with ANOVA test and no significant difference was found statistically. As a result, the developed methods could be proposed to the rutin content analysis to be simple, cheap, accurate, and precise.

Key words: *Bupropion hydrochloride, Spectrophometry, Potentiometry, Conductometry, Method validation, Tablet analysis*

Bupropion Hidroklorür'ün Orjinal UV- ve 2. Türev UV Spektrofotometri, Potansiyometri ve Kondüktometri Yöntemleri ile Farmasötik Dozaj Formlarındaki Tayini

Bupropion hidroklorür'ün (BUP) farmasötik tabletlerindeki tayini için spektrofotometrik, potansiyometrik ve kondüktometrik yöntemler geliştirilmiştir. İlk yöntem olan orjinal UV-spektrofotometri yöntemi için optimal dalgaboyu olarak 252 nm seçilmiş ve tayinlerde kullanılmıştır. İkinci türev UV spektofotometri yönteminde ise, 217.4 ve 221.8 nm dalga boylarındaki absorbans değerleri ölçülmüş ve bu ektremum değerler arasındaki uzaklık, pikten pike metodu ile hesaplanmıştır. İki spektrofotometrik yöntem de 5.72 – 20.03 µg/mL derişim aralığında valide edilmiştir. Orjinal UV-spektrofotometri yöntemi için yakalama ve tayin limiti değerleri sırasıyla, 0.75 µg/mL ve 2.28 µg/mL olarak bulunmuştur. İkinci türev UV spektofotometri yönteminde ise, bu değerler sırasıyla 0.23 µg/mL ve 0.68 µg/mL'dir. Yöntemler tam olarak valide edilmiş ve bu yöntemlerin uygulamaları BUP'un farmasötik preparatlardaki tayini için gösterilmiştir. Bunların dışında, potansiyometrik ve kondüktometrik tayin yöntemleri geliştirilmiş ve uygulamaları gösterilmiştir. Geliştirilmiş olan dört analitik yöntem ANOVA testi ile karşılaştırılmış ve aralarında istatistiksel olarak önemli bir fark olmadığı bulunmuştur. Sonuç olarak, geliştirilen yöntemler basit, ucuz, kesin ve doğru olarak rutin içerik analizleri için önerilebilir.

Anahtar kelimeler: *Bupropion hidroklorür, Spektrofotometri, Potansiyometri, Kondüktometri, Metod validasyonu, Tablet analizi*

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INTRODUCTION

Bupropion hydrochloride (BUP), (±)-2-(tert-butylamino)-3′-chloropropiophenone hydrochloride (Figure 1), is an aminoketone derivative with a pKa of 7.9 (1). It is a second generation antidepressant agent with neurochemical properties different from common tricyclic antidepressants. It has been reported that BUP is a selective inhibitor of the neuronal reuptake of catecholamines (noradrenalin and dopamine) with minimal effect on the reuptake of indolamines (serotonin) and no inhibitory effect on monoamine oxidase (2).

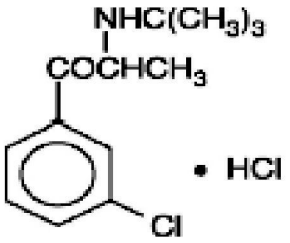

Figure 1. The chemical structure of BUP

BUP in sustained release form is used in smoking cessation as the first licensed non-nicotine pharmacological therapy. Although its exact mechanism in smoking cessation is not known, it is thought to be related to reduced reuptake of dopamine in the mesolimbic system and reduced reuptake of noradrenalin in the locus coeruleus, because nicotine is known to produce activation of the mesolimbic system, resulting in dopamine release in the nucleus accumbens (2).

Several chromatographic methods have been reported for the determination of BUP, in biological fluids including, high performance liquid chromatography (HPLC) (1, 3-6) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) (7) and in pharmaceutical preparations including HPLC (8) and TLC (9). Also chiral separation of BUP enantiomers on an ovomucoid column is described (10). Besides, using Cooper's method, BUP stability in human plasma and pharmacokinetic profiles in different animal models were studied (11, 12). A TLC method is also available for the determination of m-chlorobenzoic acid and related impurities in BUP monograph of USP XXIX (13). According to the best of our knowledge, there is no study concerning spectrophotometric, potentiometric and conductometric analysis of BUP for the determination of the drug in pharmaceutical preparations.

The aim of this study is to develop spectrophotometric, potentiometric and conductometric methods, which could be used for the determination of BUP in the pharmaceutical preparations. Spectrophotometry is well known and convenient method for the active drug content in the pharmaceutical analysis (14, 15). It has superiorities regarding simplicity, low expense of operation and reduced analysis time providing the technique suitable for satisfying the increasing demand for control and routine analysis in many fields of analytical chemistry. The validation of original UV- and second derivative UV spectrophotometric methods was investigated with respect to precision, linearity range, accuracy, limit of detection and limit of quantification obeying the suggestions of ICH guidelines (16). Potentiometric and conductometric methods are also well known and convenient methods for the active drug content in the pharmaceutical analysis. The major advantage of these methods is the direct application of suspensions and turbid samples. The specificity of the methods were demonstrated and applied to the sustained release tablets of BUP and were compared with the results of spectrophotometric methods.

EXPERIMENTAL

Reagents and chemicals

The standard BUP was obtained from Sigma (St.Louis, MO, USA). Its pharmaceutical tablet preparation is Wellbutrin SR®, a product from GlaxoSmithKline contained 150 mg active material. Methanol (gradient grade) and tablet excipients (hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, polyethylene glycol 400, povidone, maize starch, talc, titanium dioxide) were the products of Merck Co. (Darmstadt, Germany) and were all of analytical-reagent grade, therefore used with no further purification. Double distilled water used for the preparation of the solution was prepared in all pyrex glass apparatus.

Instrumentation

A Shimadzu UV-2401 PC recording double-beam UV-visible spectrophotometer with a data processing system was used. Original UV- and second derivative UV spectra of the solutions were recorded in 1 cm quartz cells at a wavelength range of 200-350 nm using slit width of 1 nm and derivation interval ($\Delta\lambda$) of 2 nm.

For potentiometric and conductometric methods, WTW Multiline P4 Universal potentiometer and conductometer cabled WTW Sen-Tix 97T combined glass pH electrode and WTW Tetracon 325 conductometric electrode cell (Germany) were used.

Procedure for Spectrophotometric Methods

Standard preparation for spectrophotometric methods

A stock solution of BUP was prepared at a concentration of 1.05 mg/mL in methanol and serially diluted with water to give working standard solution of 5.72 – 20.03 μg/mL in 2 % methanol (v/v) and 2 % methanol was used as blank solution. Original UV- and second derivative UV spectra of BUP were recorded in the range of 200-350 nm, using standard solution of 13.81 μg/mL BUP. Stock solutions and standards were all stored in glass vials covered with aluminum folia at 4 °C.

Validation studies for spectrophotometric methods

ICH guidelines were used for validation of the spectrophotometric methods with respect to precision, specificity, linearity, accuracy, limit of detection (LOD) and limit of quantification (LOQ) (16). To assess the precision of the methods, repeatability was evaluated by assaying the samples of the same concentration during the same day. Also the intermediate precision was studied by comparing the assays on different days (3 days). Five concentrations of the standard solutions (n=3) in the range of 5.72 – 20.03 μg/mL were used for the calibration curves of two spectrophotometric methods. Linearity was evaluated by linear regression analysis which bases on least squares method. Another important validation parameter, accuracy of the analytical methods were determined by analyzing both quality control samples prepared using standard BUP solution and synthetic inactive ingredients mixture by spiking with different known concentrations of BUP (within the calibration range). Standard BUP solutions were prepared at three concentration levels (5.72, 11.44, 17.15 μg/mL, n=6 for each concentration) in water and in synthetic matrix solution. Percentage recoveries, percentage error and percentage RSD values were used to express accuracy.

Quantifications were achieved by using the absorbances of BUP solutions at 252 nm, for original UV-spectrophotometric method and the distance between two peaks corresponding to the absorbance values at 217.4 and 221.8 nm for second derivative UV spectrophotometric method.

Tablet sample preparation for spectrophotometric methods

Ten Wellbutrin SR ® tablets (each contained 150 mg BUP) were weighed, net weight of each tablet calculated, and finely powdered in a mortar. A sufficient amount of tablet powder equivalent to the average weight of a tablet content was accurately weighed and 4 mL methanol was added to dissolve the active material. It was sonicated for 10 min and then the solution was centrifuged at 5000 rpm for 10 min. The supernatant was diluted as the standard solutions to achieve the spectrophotometric determinations.

Procedure for Potentiometric and Conductometric Methods

Tablet sample preparation for conductometry

The amount of tablet powder equivalent to the average weight of a tablet content was accurately weighed, 30 mL distilled water was added to dissolve the active material and titrated with 0.1000 N NaOH solution. After addition of each titrant volume, solutions were stirred for 2 min and left for 2 min to reach the equilibrium. Then the variations in the conductivity were recorded. Considering the volume change, the observed values were corrected by a dilution factor according to Equation 1.

$$\Lambda = \frac{V + v}{V} \cdot \Lambda_0 \qquad (1)$$

Λ: Corrected conductivity V : The first volume of the solution (mL)

Λ_0: Observed conductivity v : Added titrant volume (mL)

The corrected conductivity versus the added titrant volume were plotted for six times and tablet contents were calculated.

Tablet sample preparation for potentiometry

Potentiometric titrations were performed with 0.1000 N NaOH as described in conductometric titrations. After addition of each titrant volume, the variations in the pH values were recorded.

RESULTS AND DISCUSSION

Optimization of the spectrophotometric methods

It has reported that, BUP is highly soluble in water because of hydrochloride salt form (17). Thus, an organic solvent system containing methanol at a percentage of only 2 % was used for the preparation of the solutions.

UV absorbance spectrum was recorded in the range of 200-350 nm by using 13.81 μg/mL BUP solution. It was observed that a maximum appeared at 252 nm as seen in Figure 2. Thus, original UV-spectrophotometric analysis was performed at the mentioned wavelength. Also, second derivative UV spectrum was recorded in the same conditions. Two peaks were obtained at 217.4 and 221.8 nm and the distance between these extremum values was measured (Figure 3).

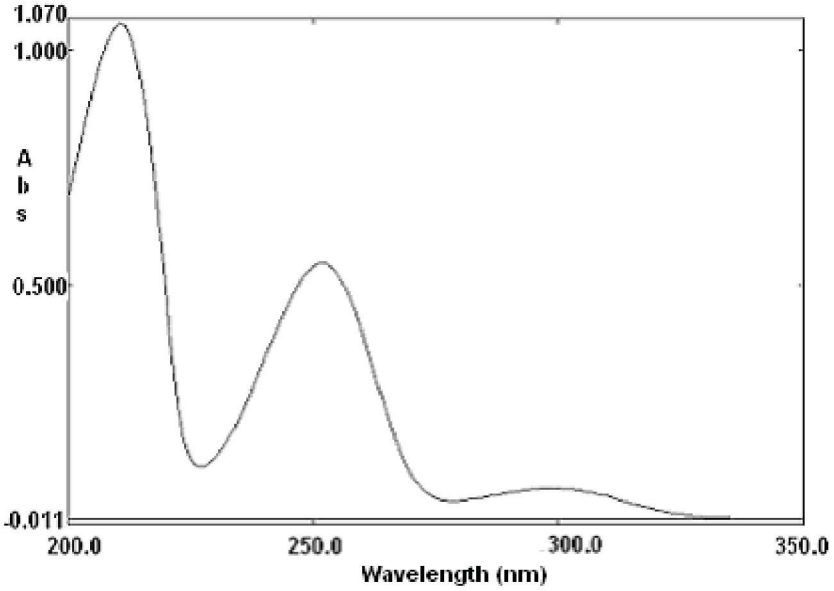

Figure 2. Original UV spectrum of BUP (13.81 µg/mL, in 2 % methanol)

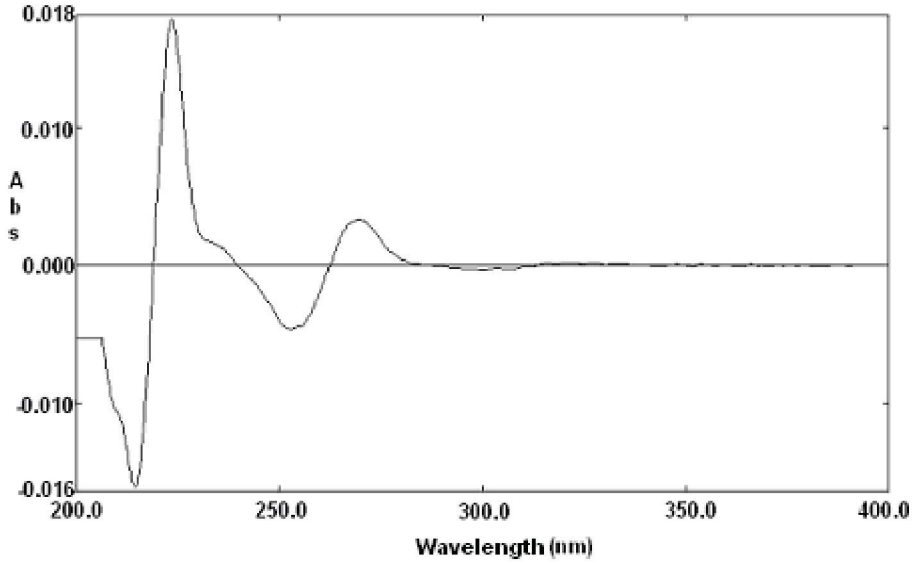

Figure 3. Second derivative UV spectrum of BUP (13.81 µg/mL, in 2 % methanol)

Method Validation for Spectrophotometric Methods

Precision

Under the optimized conditions, precision of the spectrophotometric methods were determined by repeatability (intra-day) and intermediate precision (inter-day) and were expressed as a RSD % of series of measurements. The statistically evaluated results for original UV-spectrophotometry show RSD of 0.80 indicating good intra-day precision. Inter-day variability was calculated from assays on 3 days and shows a RSD % of 0.22. The RSD values are below 2 % exhibiting the sufficient method precision and both of them are acceptable in analytical points' of view. Also, repeatability and intermediate precision were expressed for second derivative UV spectrophotometric method as RSD % of 1.91 and 5.53, respectively.

Second derivative UV spectrophotometric method exhibits good intra-day precision, in spite of the high RSD % value of inter-day precision.

Linearity

For original UV-spectrophotometry, calibration curves were constructed by plotting concentration versus the absorbances of BUP at 252 nm, and showed good linearity in the range of 5.72 – 20.03 μg/mL. Besides, the differences of the derivative absorbance values at 217.4 and 221.8 nm were used for second derivative UV spectrophotometric method in the same concentration range. The comparative results of mean linear regression equations of spectrophotometric methods for three days were tabulated in Table 1. Good correlation between absorbance values and the concentration of BUP and high correlation coefficients were obtained and the intercepts of the curves were not significantly different from zero.

Table 1. Comparative calibration results of BUP (5.72 – 20.03 μg/mL) with original UV- and second derivative UV spectrophotometric methods*.

Parameters	Original UV-spectrophotometry (day=3, n=15)	Second derivative UV spectrophotometry (day=3, n=15)
Slope, a	0.0399	0.0030
Intercept, b	-0.047	-0.0042
Correlation Coefficient, r	0.9993	0.9993
SE of slope	0.0004	0.00003
SE of intercept	0.0050	0.00044

*The results are mean linear regression equations of spectrophotometric methods for three days.

Certain analytical parameters of original UV-spectrophotometric and second derivative UV spectrophotometric methods such as limit of detection (LOD) and limit of quantification (LOQ) values were calculated as [standard deviation of intercept of regression equation/slope of regression equation] by multiplying with 3.3 and 10, respectively (16). LOD and LOQ values were found to be 0.75 and 2.28 μg/mL for original UV-spectrophotometry. By the same way, these parameters of second derivative UV spectrophotometric method were calculated as 0.23 μg/mL for LOD and 0.68 μg/mL for LOQ. As seen, lower LOD and LOQ values were obtained with second derivative UV spectrophotometric method.

Accuracy

Accuracy of two spectrophotometric methods were tested as described in experimental section and were evaluated as percentage relative error [[(found concentration-spiked concentration)/spiked concentration] x 100%], and precisions were evaluated by the coefficient of variation (C.V. %, RSD %, [SD/mean x 100]) at the low, central and high concentration levels of linearity range. The percent recoveries were found almost 100 % for drug substance and drug product and accuracies were much less than the acceptance criteria. The same concentration levels were used to evaluate precisions as degree of repeatability. The values of RSD % were also much less than the acceptance criteria showing good precision of the proposed methods as seen in Table 2 and 3.

Table 2. The results of method accuracy of standard BUP and BUP spiked matrix with original UV-spectrophotometry.

Added BUP (μg/mL)	Found BUP (μg/mL) (mean±SD, *n=6*)	Recovery (%)	Accuracy (%)	RSD (%)
5.72	5.72 ± 0.036	99.43	-0.48	0.63
11.44	11.27 ± 0.097	98.52	-1.45	0.86
17.15	16.93 ± 0.099	98.65	-1.29	0.58
BUP spiked to matrix (μg/mL)	Found BUP (μg/mL) (mean±SD, *n=6*)	Recovery (%)	Accuracy (%)	RSD (%)
5.72	5.80 ± 0.019	101.34	1.34	0.35
11.44	11.55 ± 0.030	100.94	0.94	0.25
17.15	17.15 ± 0.055	99.95	-0.05	0.32

Table 3. The results of method accuracy of standard BUP and BUP spiked matrix with second derivative UV spectrophotometry.

Added BUP (μg/mL)	Found BUP (μg/mL) (mean ± SD, *n=6*)	Recovery (%)	Accuracy (%)	RSD (%)
5.72	5.69 ± 0.083	99.40	-0.60	1.47
11.44	11.30 ± 0.18	98.84	-1.21	1.60
17.15	16.80 ± 0.14	97.91	-2.09	0.80
BUP spiked to matrix (μg/mL)	Found BUP (μg/mL) (mean ± SD, *n=6*)	Recovery (%)	Accuracy (%)	RSD (%)
5.72	5.66 ± 0.10	98.81	-1.19	1.87
11.44	11.30 ± 0.18	98.84	-1.16	1.60
17.15	17.40 ± 0.21	101.44	1.44	1.20

Specificity

Specificity was performed using tablet inactive ingredients to assure that these common tablet dosage form ingredients could be interfered. The data indicated that these ingredients did not interfere with BUP and the wavelength of maximum absorbance has not been changed according to both original UV and derivative UV spectrum. Thus, the specificity of the proposed methods was considered good for the application of the methods in tablet analysis.

Potentiometric and Conductometric Methods

For the conductometric titrations, the corrected conductivity versus the added titrant volume was plotted and two linear branches with high correlation coefficients were obtained as seen in Figure 4. The end point in conductometric titrations was obtained by extrapolation of these branches of the plot. Titrations were repeated six times and very close end point values (5.86 ± 0.1) were obtained. From these end points, tablet contents were calculated.

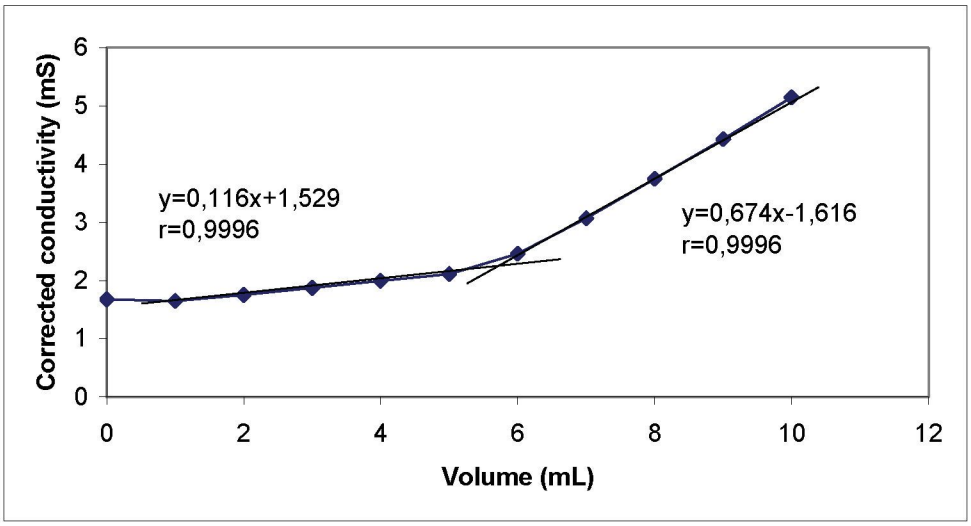

Figure 4. Conductometric titration curve of BUP tablets with 0.1000 N NaOH solution.

After conductometric titrations, by plotting the pH values versus the added titrant volume, a well defined S-shape potentiometric curve was obtained as seen in Figure 5a. First and second derivative values of pH were calculated and plotted versus the added titrant volume (Figure 5b and Figure 5c). Titrations were repeated six times and very close end points (6.00 ± 0.07) were obtained as in conductometric titrations. From these end points, tablet contents were calculated.

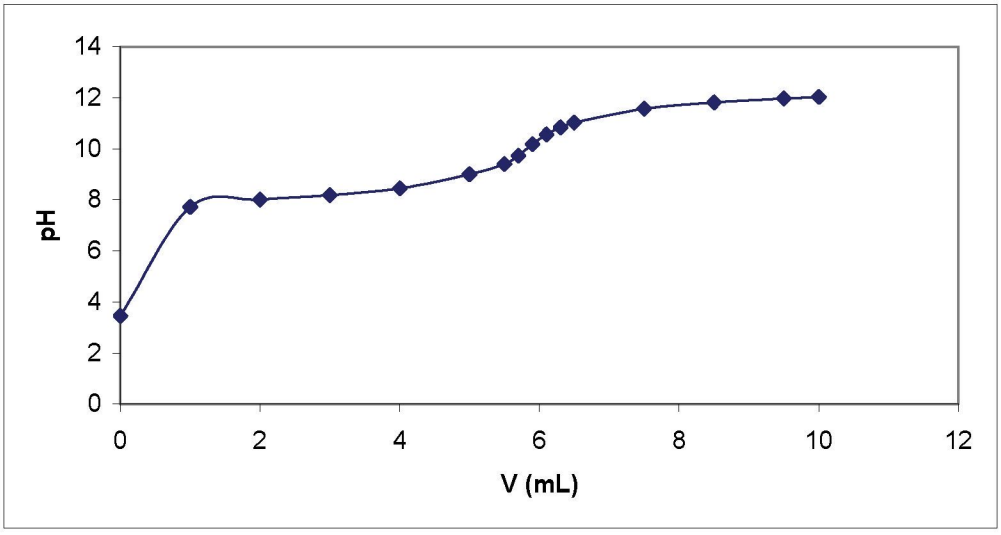

Figure 5a. Potentiometric titration curve of BUP tablet solution with 0.1000 N NaOH.

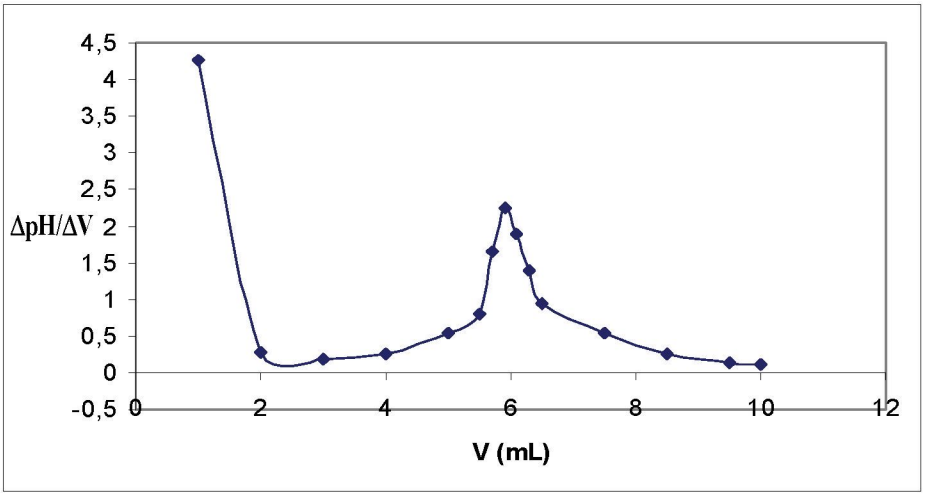

Figure 5b. First derivative potentiometric curve of BUP tablet solution with 0.1000 N NaOH.

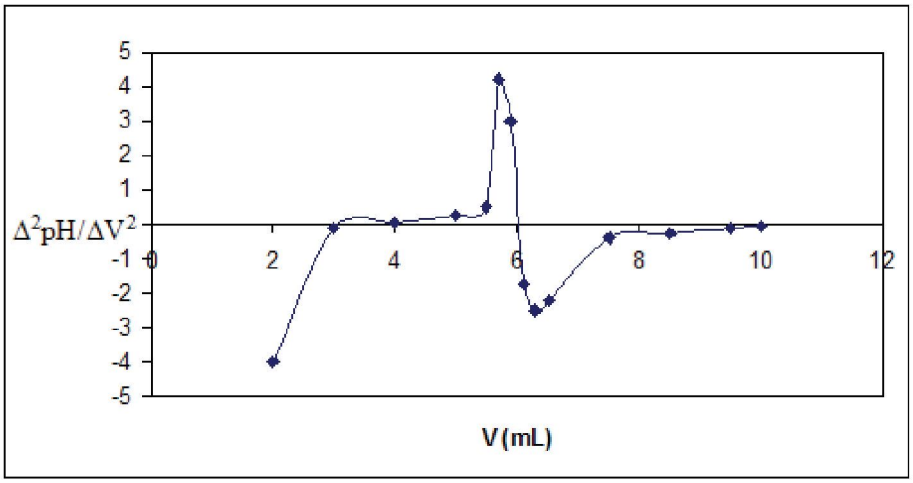

Figure 5c. Second derivative potentiometric curve of BUP tablet solution with 0.1000 N NaOH

Application of the Proposed Methods to Pharmaceuticals

The application of the developed methods were performed in pharmaceutical tablets of BUP containing 150-mg active material as described in the experimental section. The spectrum of tablet samples carried the characteristics of standard BUP and no interference was originated from the matrix was observed for both spectrophotometric methods. The compared results for the tablet analysis of BUP obtained by original UV- and second derivative UV spectrophotometry are given in Table 4.

Table 4. The results of tablet analysis of BUP performed by original UV-spectrophotometry and second derivative UV spectrophotometry (Label claim is 150 mg BUP/tablet)

	Original UV-spectrophotometry	Second derivative UV spectrophotometry
Mean ± SD (n=6)	162.4 ± 4.72	161.1 ± 3.66
% RSD	2.90	2.27
t-test ($p<0.05$)	0.67	Table $t_{0.05}$=2.57
F-test ($p<0.05$)	1.66	Table $F_{0.05}$=5.05

Also, tablet analysis of potentiometric and conductometric methods were compared as seen in Table 5.

Table 5. The results of tablet analysis of BUP performed by potentiometric and conductometric methods (Label claim is 150 mg BUP/tablet)

	Potentiometry	Conductometry
Mean ± SD (n=6)	164.9 ± 1.39	164.5 ± 2.84
% RSD	0.84	1.73
t-test ($p<0.05$)	0.70	Table $t_{0.05}$=2.57
F-test ($p<0.05$)	4.17	Table $F_{0.05}$=5.05

Besides, all the methods were compared statistically with ANOVA test. It is informative to show the difference of mean values of samples obtained with the proposed methods by comparing the variances of the sample groups. Insignificant differences among the methods were obtained at the 95 % probability level ($F_{4,23}$=1.902, $p<0.05$). The contents are all in the limits of USP XXIX suggestions (13).

CONCLUSION

Simple spectrophotometric, potentiometric and conductometric methods for the determination of BUP in pharmaceuticals were developed in this study. Shorter analysis times of spectrophotometric methods allow rapid determination of the drug, which is important for routine analysis. The linearity range, limits of detection and quantification, precision and accuracy were processed to determine the suitability of the spectrophotometric methods and the confirmed results were obtained also, the specificity of potentiometric and conductometric methods were demonstrated. Although, spectrophotometry is not a selective method, it has the advantage of lower consumpsion of expensive and harmful organic solvents. In the proposed methods the analysis time is quite short with a simple procedure and also better limits of detection and quantification results were obtained with derivative UV spectrophotometry compared to original UV-spectrophotometric method. Also, potentiometric and conductometric titration methods were developed and the tablet results of these methods were compared with spectrophotometric methods. Potentiometric and conductometric titration methods have superiorities regarding the direct application of suspensions and turbid samples and no need to time-consuming sample preparation steps. All the developed methods are simple, rapid, reliable, cost effective and can be proposed for routine analysis laboratories and quality control purposes.

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