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ALPTUG ATILA
YUCEL KADIOGLU

Department of Analytical Chemistry, Faculty of Pharmacy, Ataturk University, Erzurum, Turkey

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DETERMINATION OF PRILOCAINE HCl IN BULK DRUG AND PHARMACEUTICAL FORMULATION BY GC-NPD METHOD

A novel analytical method was developed and validated for determination of prilocaine HCl in bulk drug and pharmaceutical formulation by gas chromatography-nitrogen phosphorus detection (GC-NPD). The chromatographic separation was performed using a HP-5MS column. The calibration curve was linear over the concentration range of 40-1000 ng ml^{-1} with a correlation coefficient of 0.9998. The limits of detection (LOD) and quantification (LOQ) of the method were 10 and 35 ng ml^{-1}, respectively. The within-day and between-day precision, expressed as the percent relative standard deviation (RSD%) were less than 5.0%, and the accuracy (percent relative error) was better than 4.0%. The developed method can be directly and easily applied for determination of prilocaine HCl in bulk drug and pharmaceutical formulation using internal standard methodology.

Keywords: GC-NPD, prilocaine HCl, pharmaceutical formulation, validation.

Local anesthetic drugs are mainly used to reversibly block nerve function in various local or regional treatments. They play an important role clinically in dentistry and minor surgery for temporary relief of pain [1,2]. Prilocaine, 2-propylamino-*N*-*o*-tolil-propiyonamit hydrochloride (Figure 1A), is a local anesthetic of the amide type [3]. Prilocaine, unlike other amide anesthetics, is a secondary amino derivative of toludine. It produces less vasodilation and toxicity than lidocaine and is considered relatively free from an allergic reaction [4]. Prilocaine is extensively metabolized by the liver. Prilocaine's primary limiting factor clinically is the production of methemoglobinemia, a side effect caused by its metabolite *o*-toludine [5,6].

Several methods have been reported for determination of prilocaine HCl in biological samples and pharmaceutical formulations including the capillary electrophoresis method [3], HPLC with different detection [5,6-16], liquid chromatography-tandem mass spectrometry [17], sequential injection chromatography with Franz cell [18], adsorptive square wave method [19] and spectrophotometry method [20]. In addition, the determination of mixtures with other local anesthetics of prilocaine HCl in biological samples have been done with GC-MS [21,22] and GC methods [23-29].

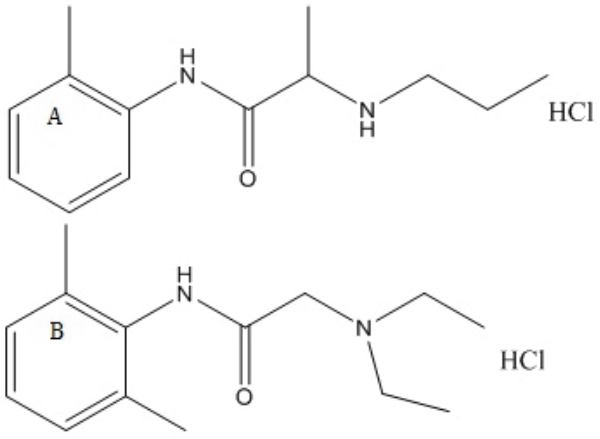

Figure 1. Chemical structure of: A) prilocaine HCl; B) IS (lidocaine HCl).

So far, according to our present knowledge, no GC-NPD method for the analysis of prilocaine HCl alone in any pharmaceutical formulations is available

Correspondence: Y. Kadioglu, Department of Analytical Chemistry, Faculty of Pharmacy, Ataturk University, 25240, Erzurum, Turkey.
E-mails: yucel@atauni.edu.tr ; yucelkadi@yahoo.com
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in the literature. The development a selective and effective method for drug analysis is important for keeping abreast of therapeutic and toxic effects in biological samples and quality controlling studies in pharmaceutical formulations. The aim of the present work is to develop and validate a new GC-NPD method for determination of prilocaine HCl in pharmaceutical formulation with a simple sample preparation using internal standard methodology. The proposed method was validated with validation parameters, which are sensitivity, specificity, linearity, precision, accuracy, stability and analytical recovery in accordance with International Conference on Harmonization (ICH) guidelines [30].

EXPERIMENTAL

Materials and reagents

Prilocaine HCl, which was used as the reference substance (99.9% purity), was supplied by Novartis Pharmaceutical Industry (Ankara, Turkey). Lidocaine HCl (99.8% purity), which was used as the internal standard (IS; Figure 1B), was supplied by the Doping Control Center of Hacettepe University (Ankara, Turkey). High-purity grade methanol and all other reagents were purchased from Merck (Germany). All gases were supplied by Havas (Ankara, Turkey).

The following pharmaceutical formulation of prilocaine HCl was obtained from local sources in Erzurum (Turkey): Citanest® injection (2% flacon, Astra Zeneca A.S., Turkey) containing prilocaine HCl, parahydroxybenzoate and sodium chloride with the concentration of 20, 1 and 0.46 mg ml^{-1}, respectively.

Equipment

The chromatographic analysis was performed by an HP 6890 Series II gas chromatography system equipped with an HP 7673 auto sampler, HP automatic injector (Model 7673), HP 5890 nitrogen-phosphorus detector (NPD) and HP software.

Chromatographic conditions

Chromatographic separation was achieved using an HP-5MS column (25 m×0.2 mm i.d.×0.33 μm film thickness, cross-linked [% phenyl-methylpolysiloxano, Germany). The split mode (10:1) was used and the flow rate of the carrier gas (helium) was kept constant at 0.7 ml min^{-1} during the analysis. Hydrogen (4 ml min^{-1}) and dried air (60 ml min^{-1}) were used as auxiliary gases for the detector (NPD). The injector volume was 3.0 μl. The injector and detector temperatures were 250 °C. The oven temperature programs were as follows: initial temperature of 80 °C, then ramp rate of 15 °C min^{-1} and final temperature of 300 °C, where the temperature was held for 4 min. The chromatograms obtained in these operating conditions for standard solutions, are shown in Figure 2.

Preparation of standard solutions

The standard working (SW) solutions (40, 100, 250, 500, 750 and 1000 ng ml^{-1}) and quality control (QC) samples (100, 250 and 500 ng ml^{-1}) were prepared in methanol from stock solution (100 μg ml^{-1}). All solutions were prepared daily and stored at -20 °C when not in use.

SW solution of lidocaine HCl (internal standard, IS) was prepared at 100 ng ml^{-1} concentration with methanol from the stock solution (50 μg ml^{-1}).

Preparations of pharmaceutical formulation

Prilocaine (Citanest® flacon) is a drug that is injected during various surgical or dental procedures. The content of a flacon was mixed into a volumetric flask and an aliquot of the solution equivalent to 20 mg prilocaine HCl was quantitatively transferred to a

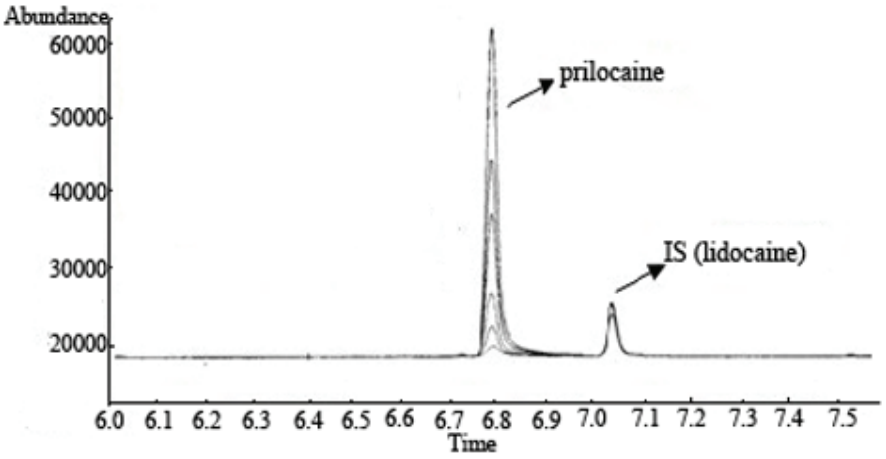

Figure 2. GC-NPD Chromatogram of standard solutions (40, 100, 250, 500, 750 and 1000 ng ml^{-1}) of prilocaine and IS (100 ng ml^{-1}).

50 ml calibrated measuring flask and made up to the mark with methanol. The solution was filtered through a 0.22 μm Millipore filter. The filtrate was diluted with methanol to obtain a 150 ng ml^{-1} concentration of prilocaine HCl for pharmaceutical formulation.

About 100 ng ml^{-1} concentration of IS was added into the solution prepared from the flacon. The solution was analyzed as described in the section Chromatographic conditions.

Data analysis

All statistical calculations were performed with the Statistical Product and Service Solutions (IBM SPSS) for Windows, version 20.0. Correlations were considered statistically significant if the calculated P values were 0.05 or less.

RESULTS

Specificity

Specificity should confirm the ability of the method to unequivocally assess the analyte in the presence of other components that may be present (for example: impurities, degradation products and matrix components). The specificity of method was demonstrated by the representative chromatograms for prilocaine HCl and lidocaine HCl (IS) in standard solutions shown in Figure 2. The retention time of prilocaine HCl and lidocaine HCl was 6.78 min and 7.22 min. Different temperature programs were investigated for the exception of matrix interference. At the end of this investigation, the best temperature program was selected for a good resolution and thus the all experiments was used the oven temperature program described at section Chromatographic conditions. When the ramp rate was more or less than 15 °C min^{-1}, good resolution of the peaks (analyte peak and matrix interference peaks) was not obtained.

Linearity

Linearity was established over a linear range of 40-1000 ng ml^{-1} at six concentrations with a constant concentration of IS (100 ng ml^{-1}). The calibration curve was constructed by plotting the ratio of the peak areas of prilocaine HCl and IS, versus the concentrations of prilocaine HCl (Figure 3). The linear regression equation and statistical parameters were calculated by the least squares method using Microsoft Excel® and summarized in Table 1. Relative residual standard deviation ($S_{\Delta y/y,n-2}$) is also included in the table [31].

Limit of detection and quantification

The limit of detection (LOD) is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated as an exact value. The limit of quantification (LOQ) is the lowest amount of analyte that can be quantitatively determined with suitable precision [30]. The LOD and LOQ values of the developed method were determined as 3:1 and 10:1 of the signal/noise ratio, respectively, by injecting progressively low concentration of the standard solution under the chromatographic conditions. These values are also listed in Table 1.

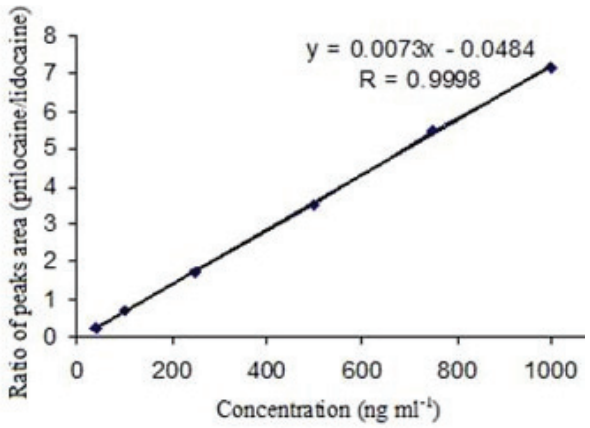

Figure 3. Calibration curve for determination of prilocaine HCl with proposed method.

Table 1. Results of regression analysis of prilocaine HCl

Parameter	GC-NPD
Linearity, ng ml^{-1}	40-1000
Regression equation[a]	$y = 0.0073x-0.0484$[b]
Standard deviation of slope (*Sa*)	5.4×10^{-4}
Standard deviation of intercept (*Sb*)	2.8×10^{-2}
Correlation coefficient	0.9998
Standard deviation of correlation coefficient	0.0045
Relative residual standard deviation ($S_{\Delta y/y, n-2}$)	0.059
Limit of detection (*LOD*), ng ml^{-1}	10
Limit of quantification (*LOQ*), ng ml^{-1}	35

[a]Average of six replicate determinations; [b]*y*: peak-area ratios (prilocaine/IS), *x*: prilocaine concentration

Precision and accuracy

Assay precision was determined by repeatability (within-day) and intermediate precision (between-day). The within-day was evaluated by assaying samples, at same concentration and during the same day. The between-day was studied by comparing the assay on different six days. The accuracy of this analytic method was evaluated by checking at three different concentrations of prilocaine HCl with IS. The precision of method was given as the relative standard deviation [RSD % = (100×standard deviation)/mean] and the accuracy of method was given with percent relative error [RE% = (found concentration - known concentration)×100/known concentration]. The RSD % values for within-day and between-day precision of proposed method were found to be ≤4.9%. The RE% for within-day and between-day accuracy for method were found to be ≤3.8%. Precision and accuracy studies in pharmaceutical formulation showed acceptable RSD % and RE % values. The results are shown in Table 2.

Analytical recovery

In order to double-check the accuracy of the proposed method, the recovery study was performed in two different ways. In first method, the standard addition technique was used. The three different concentrations (100, 250 and 500 ng ml^{-1}) of standard sample were added to 150 ng ml^{-1} concentration of solution of pharmaceutical formulation and assayed with GC-NPD method. The analytical recovery values of proposed method were calculated from followed equation:

$$\text{Analytical recovery, \%} = 100[(C_t-C_u)/C_a]$$

where C_t is total concentration of the analyte determined; C_u is the concentration of the pure analyte added to the formulation; C_a is the concentration of the analyte present in the formulation. The average percent recoveries were determined between 98.6 and 99.6% for proposed method, indicating good accuracy of the method. No interference from the common excipients was observed. The RSD % values of recovery were found to range from 0.9 to 1.4% (Table 3).

In the second method, the technique of proportioning was used. The solutions in three different concentrations (100, 250 and 500 ng ml^{-1}) from pharmaceutical formulation were prepared and assessed with same procedures. The percent recovery values were calculated from followed equation for each case: Recovery % = $100(C_{found}/C_{formulation})$. The average recovery values for second method were determined between from 100.1 and 98.8%. The RSD % values of recovery were found to range from 1.9 to 1.2% (Table 3).

The recovery values of both methods were compared statistically by the One-Sample *t*-test at 95% confidence level with five degrees of freedom. The *t*-values were obtained as $t = 529.2$ for the first method and $t = 415.5$ for the second method. There was no significant difference between both recovery methods ($p > 0.05$).

Interferences study

The effects of common excipients and additives were tested for their possible interferences in the assay of prilocaine HCl. In addition to the active ingredient, prilocaine HCl, flacon contains the following inactive ingredients: methyl para-hydroxybenzoate and sodium chloride. No interference of these substances at the levels found was determined in dosage forms.

Stability

Stability studies were performed on pharmaceutical formulation and standard solutions of prilocaine HCl (250, 500 and 750 ng ml^{-1}) and these solutions were stored at 4 °C (refrigerator), room temperature and auto sampler at 24, 48 and 72 h time and then changes in concentration of standard solutions and pharmaceutical formulation under conditions of the study were evaluated using the GC-NPD method. One set of these solutions was assayed immediately and taken as the standard (100%). The stock solution of prilocaine HCl was found to be stable for three month. Standard solutions of prilocaine HCl and pharmaceutical solution were found to be stable for 48 h at room temperature and on auto sampler. After 72 h at

Table 2. Precision and accuracy of GC-NPD method

Added ng ml^{-1}	Within-day			Between-day		
	Found±SD[a] ng ml^{-1}	Precision[b] RSD, %	Accuracy[c] RE, %	Found±SD[a] ng ml^{-1}	Precision[b] RSD, %	Accuracy[c] RE, %
100	103.3±2.7	2.6	3.3	101.1±5.0	4.9	1.1
250	251.9±2.6	1.0	0.8	250.8±8.6	3.4	0.3
500	480.9±9.5	2.0	-3.8	495.7±8.9	1.8	-0.9

[a]SD: standard deviation of six replicate determinations, [b]RSD: relative standard deviation, [c]RE: relative error

Table 3. Analytical recovery values with two ways of performing the proposed method

Technique	Amount added ng ml^{-1}	Amount taken[a] ng ml^{-1}	Total amount found, mean±*SD* ng ml^{-1}	Recovery %	*RSD* %
The standard addition technique	100	150	248.9±2.8	99.3	1.1
	250		397.9±5.7	98.6	1.4
	500		649.4±6.1	99.6	0.9
The technique of proportioning	-	100	98.8±1.9	98.8	1.9
		250	250.2±4.4	100.1	1.8
		500	497.8±5.8	99.6	1.2

[a]Solutions of pharmaceutical preparation, [b]average of six replicate determinations

room temperature and auto sampler, it was observed that prilocaine converted to its metabolite (*o*-toluidine) (Figure 4). Because of its chemical structure, prilocaine is readily hydrolyzed in alcohol medium. The formation of *o*-toluidine as a major degradation product in solutions of prilocaine HCl was checked by spiking of the standard solution of *o*-toluidine. *o*-Toluidine could be formed during degradation of prilocaine HCl, based on the information in the literature that amide anesthetics were degraded to *o*-toluidine with temperature change [5,14].

Application of method for analysis of pharmaceutical formulation

The proposed method was evaluated in the assay of commercially available flacon containing prilocaine HCl 400 mg/20 ml (Citanest® flacon). Evaluation was performed using the calibration curve method, since no significant difference between the slopes of the calibration curves for pharmaceutical formulation and standard solutions was observed. The amount of flacon containing 400 mg prilocaine HCl per 20 mL was determined in six replicates. The results obtained are satisfactorily accurate and precise as indicated by the excellent % recovery and *SD* < 4.25 (Table 4). The experiments showed that there was no interference from the additions and excipients. The determination was repeated six times, and the final obtained recovery of the formulation was approximately 98.9%, with an RSD % of 1.07.

Table 4. Determination of prilocaine HCl in flacon (400 mg prilocaine HCl/20 ml)

Pharmaceutical formulation	Found±*SD*[a] mg	Recovery %	RSD %	Confidence interval
Citanest® injection (2% flacon)	395.6±4.25	98.9	1.07	98.0-99.9

[a]Average of six replicate determinations

DISCUSSION

In the present study, a highly selective gas chromatography (GC) with nitrogen-phosphorous detection (NPD) that enabled us to quantify the prilocaine HCl without derivatization in pharmaceutical formulation was developed and validated. Prilocaine HCl is one of local anesthetic substances. Chromatographic

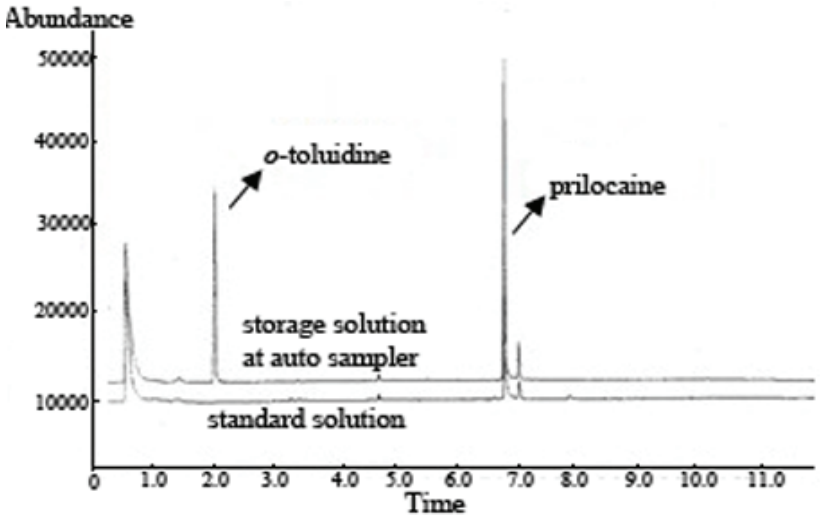

Figure 4. GC Chromatogram of prilocaine and o-toluidine formed during storage at auto sampler during 72 h period.

analyses of pharmaceutical compounds have evolved as drug industry matured. Gas-liquid chromatography (GLC) developed in the early 1950s to the present with many concurrent innovations in chromatography columns and detection systems [32]. Gas chromatography has found its niche in the monitoring of certain impurities, measuring and characterizing excipients, preservatives, and active drugs. In assays where sensitivity is required, gas chromatographic methods are still unsurpassed [32]. An important aspect of the implementing a new assay in routine quality control analysis is that it should be thoroughly evaluated before introduction for routine use. GC with different detections can be considered a very appropriate method for analysis of local anesthetic substances that these are very volatile substances. The proposed method has supplied all the requirements in terms of accuracy, linearity, recovery and precision that could be accepted as a reliable and applicable method. The precision of method was adequate, because the RSD values were less than 5.0%. The accuracy of method (RE) was less than 4.0%. There are several advantages of this method, namely high specificity, good accuracy and precision values, short chromatographic run time (7.5 min). In the chromatograms taken with proposed method, the following peaks: prilocaine HCl with retention time approximately 6.78 min; lidocaine HCl (IS) with retention time approximately 7.22 min and the degradation product *o*-toluidine with retention time of approximately 2.15 min (Figures 2 and 4), were identified. Under the described chromatographic conditions (Figure 3), a linear relationship between the peak-area ratio (y = prilocaine peak area/IS peak area) and analyte (prilocaine) concentration (x) were obtained (Table 1). In addition to these, the analytical recovery percentage of proposed method is high.

There are many preparations for local anesthesia on the pharmaceutical market, in which prilocaine and lidocaine can occur as active substances. Both drugs were served as the internal standard for each other. Prilocaine used in anesthetic practice is less toxic than lidocaine. *o*-Toluidine is a metabolite of prilocaine. Prilocaine metabolizes to *o*-toluidine during biotransformation, which many oxidize hemoglobin to methemoglobin and also *o*-toluidine has been shown to be carcinogenic in laboratory animals in the National Toxicology Program (NTP) studies [33]. *o*-Toluidine can be potential technological impurities of medicinal products because they are used as substrates in the synthesis of pharmaceuticals. In addition, the hydrolysis of the amide linkage of prilocaine results in the formation of decomposition product *o*-toluidine during storage of drugs containing prilocaine [5,14,33]. After 72 h storage of standard solutions of prilocaine and pharmaceutical formulation, it was observed that prilocaine was converted to its metabolite (*o*-toluidine). The content of *o*-toluidine in standard solutions and pharmaceutical formulation chosen for this study was determined by the standard addition method, while the content of local anesthetics in pharmaceutical formulation studied was assayed by GC-NPD method.

CONCLUSION

In this study, a new GC-NPD method was developed to provide a very sensitive and quantitative assay of prilocaine HCl in bulk drug and pharmaceutical formulation. In addition, *o*-toluidine was determined in stability studies. The analysis and preparation of samples was performed in a relatively short time. The method can be applied in routine quality control analysis of pharmaceutical formulations and clinical laboratories.

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ALPTUG ATILA
YUCEL KADIOGLU

Department of Analytical Chemistry, Faculty of Pharmacy, Ataturk University, Erzurum, Turkey

NAUČNI RAD

ODREĐIVANJE PRILOKAIN HIDROHLORIDA U FARMACEUTSKOJ SUPSTANCI I PREPARATIMA METODOM GC-NPD

Razvijena je i validirana nova metoda za određivanje prilokain-hidrohlorida u farmaceutskoj supstanci i preparatima metodom GC-NPD. Hromatografsko razdvajanje je izvršeno kolonom HP-5MS. Kalibraciona kriva je bila linearna u opsegu koncentracije 40-1000 ng/ml, sa koeficijentom korelacije 0,9998. Limit detekcije (LOD) i limit kvantifikacije (LOQ) ove metode su bili10 i 35 ng/ml, redom. Preciznost metode u toku dana i različitim danima, izražena kao procentna relativna standardna devijacija, bila je manja od 5%, dok je tačnost metode (procentna relativna greška) bila manja od 4%. Razvijena metoda se može direktno i lako primeniti za određivanje prilokain-hidrohlorida u farmaceutskoj supstanci i preparatima koristeći internu standardnu metodologiju.

Ključne reči: GC-NPD, prilokain-hidrohlorid, farmaceutski preparati, validacija.