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RESEARCH ARTICLE

Method Development for Analysis of Lidocaine Hydrochloride in Pharmaceutical Dosage Form by HPLC

Rizoana Haque Nisa[1], Aminul Islam[2], Anika Zafreen[3], Sadia Islam[4], Md. Ashiqur Rahman[5,*]

[1] *Rizoana Haque Nisa, State University of Bangladesh, Dhaka, Bangladesh*
[2] *Aminul Islam, State University of Bangladesh, Dhaka, Bangladesh*
[3] *Anika Zafreen, Novus Clinical Research Services Limited, Dhaka, Bangladesh*
[4] *Sadia Islam, Bangladesh Specialized Hospital PLC, Bangladesh*
[5] *Md. Ashiqur Rahman, Novus Clinical Research Services Limited, Dhaka, Bangladesh*
*** Corresponding author:** Md. Ashiqur Rahman, ararashiqur@gmail.com

ABSTRACT

Background: Accurate quantification of lidocaine in pharmaceutical products is crucial to ensure proper dosage, as incorrect concentrations can lead to therapeutic failure or adverse effects. High-performance liquid chromatography (HPLC) is the preferred method due to its precision and ability to separate complex mixtures. However, challenges remain in ensuring reproducibility and robustness, especially in formulations with excipients or impurities. Validating these methods is essential for reliable results. **Aim of the Study:** This study aims to develop and validate an HPLC method for quantifying lidocaine hydrochloride in pharmaceutical forms. The focus is on optimizing chromatographic parameters and validating the method based on ICH guidelines to ensure reliable, consistent results for quality control. **Materials and Methods**: The study was conducted at the Centre of Advanced Research in Sciences, Dhaka University, using lidocaine hydrochloride (HPLC standard) and a local market sample. HPLC-grade methanol and Milli-Q water were used for solution preparation. A Shimadzu UV/Visible spectrophotometer and Shimadzu UFLC Prominence HPLC system with a C-18 column were used for analysis. The chromatographic conditions included a 50:50 methanol-water mobile phase, 1 mL/min flow rate, and 250 nm detection wavelength. Lidocaine stock solutions were prepared, and calibration curves were created using standard concentrations. For the gel sample, 50 mg of 2% lidocaine gel was dissolved in methanol and sonicated, followed by filtration and analysis. The λ max of lidocaine was determined to be 263 nm. **Results**: Stock solutions of lidocaine hydrochloride were prepared in 0.1M HCl, ethanol & water (1:99), and methanol & water (50:50). The λ max was found to be 263 nm for all preparations, and a calibration curve was constructed using standard concentrations (5–25 µg/ml) in 0.1M HCl, showing a linear relationship ($R^2 = 0.998$). For the HPLC analysis, a standard stock solution (100 µg/ml) of lidocaine was prepared in methanol. Working solutions were prepared with concentrations ranging from 20 to 60 µg/ml, and the retention time was 2.6 minutes. A calibration curve was plotted based on the average area values for each concentration, showing linearity ($R^2 = 0.998$). The market lidocaine gel was analyzed, revealing a

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concentration of 35.69 μg/ml, which is higher than the declared value of 20 mg per gram (2% concentration). The retention time of the sample matched that of the standard (2.6 minutes), confirming the presence of lidocaine. This higher-than-expected concentration may result from an improper extraction procedure or impurities in the formulation, potentially leading to elevated side effects despite being applied topically. **Conclusion**: A simple, rapid, and sensitive RP-HPLC method was developed for determining lidocaine hydrochloride in pharmaceutical forms. This cost-effective method is suitable for quality control in pharmaceutical and cosmetic products.

Keywords: RP-HPLC; lidocaine hydrochloride; pharmaceutical analysis; sensitivity

1. Introduction

Local anesthetics are pharmaceutical agents that reversibly block nerve conduction when applied locally, preventing the transmission of sensory impulses to the central nervous system (CNS). These drugs play a crucial role in medical and dental procedures by inducing temporary loss of sensation in a specific area without causing systemic effects or unconsciousness[1]. Among the most commonly used local anesthetics are lidocaine, bupivacaine, ropivacaine, and procaine. Lidocaine, in particular, stands out due to its rapid onset of action, high efficacy, and relatively low toxicity profile[2]. Beyond its primary use as an anesthetic, lidocaine also serves as an antiarrhythmic agent in the management of ventricular arrhythmias, further highlighting its clinical importance[3].

The chemical structure of local anesthetics consists of three key components: an aromatic ring (lipophilic), an intermediate chain, and an amine group (hydrophilic)[4]. This structural configuration allows the drug to interact with sodium channels in nerve membranes, inhibiting depolarization and blocking pain signal transmission. Based on their chemical linkage, local anesthetics are classified into two major groups: amino esters (e.g., procaine, cocaine, tetracaine) and amino amides (e.g., lidocaine, bupivacaine, ropivacaine) [5]. Amino amides, such as lidocaine, exhibit greater stability in solution and undergo hepatic metabolism, whereas amino esters are hydrolyzed by plasma cholinesterases and are more likely to cause hypersensitivity reactions[6].

Lidocaine hydrochloride, a prototypical amino amide local anesthetic, is available in various pharmaceutical formulations, including injectable solutions, topical gels, sprays, ointments, and transdermal patches[7]. Its versatility in administration routes makes it indispensable in clinical settings, ranging from minor surgical procedures to pain management in chronic conditions. The drug's efficacy depends on several physicochemical properties, including lipid solubility, protein binding affinity, and degree of ionization at physiological pH. These factors influence its onset of action, duration of effect, and overall pharmacokinetic profile[8].

Ensuring the quality, potency, and purity of lidocaine hydrochloride in pharmaceutical formulations is critical for patient safety and therapeutic efficacy. High-performance liquid chromatography (HPLC) has emerged as a gold-standard analytical technique for drug quantification due to its high sensitivity, selectivity, and reproducibility[9]. HPLC is particularly well-suited for the analysis of lidocaine because it enables efficient separation and accurate quantification of the drug in complex matrices, even at low concentrations. The technique relies on the differential partitioning of analytes between a stationary phase and a mobile phase, allowing for precise resolution of lidocaine from potential impurities or degradation products[10].

This study focuses on the development and validation of a robust HPLC method for the quantitative analysis of lidocaine hydrochloride in pharmaceutical dosage forms. The method optimization process involves systematic evaluation of chromatographic parameters, including mobile phase composition, column

selection, flow rate, and detection wavelength. By employing a reversed-phase HPLC (RP-HPLC) approach with a C18 column and a UV detector, the method achieves high resolution and reproducibility. The validation protocol adheres to International Council for Harmonisation (ICH) guidelines, assessing parameters such as linearity, precision, accuracy, specificity, and robustness to ensure method reliability

2. Literature review

Lidocaine, a local anesthetic commonly used in various pharmaceutical formulations, has been the subject of multiple studies focusing on its analysis, particularly in combination with other active ingredients. Several methods have been developed for the simultaneous determination of lidocaine in pharmaceutical preparations, such as gel formulations, ointments, and ear drop solutions[11]. This section reviews different analytical approaches used to quantify lidocaine and other active ingredients in combined dosage forms, highlighting the advancements and challenges in its analysis[12].

A stability-indicating high-performance liquid chromatography (HPLC) method using diode array detection (DAD) was developed for the simultaneous determination of miconazole nitrate (MZ) and lidocaine hydrochloride (LD) in a combined oral gel[13]. The chromatographic separation was achieved using a Zorbax SB-C8 column with a mobile phase composed of 0.05M phosphoric acid and acetonitrile. The gradient elution was optimized to separate the two drugs effectively, with retention times of approximately 4.1 minutes for lidocaine and 8.4 minutes for miconazole nitrate[14]. The method was validated for various parameters, including linearity, accuracy, precision, and robustness, making it a reliable tool for the analysis of this pharmaceutical combination. It also proved effective in resolving forced-degradation products and potential impurities[15].

A study developed and validated two methods for the analysis of a ternary mixture containing lidocaine, phenylephrine, and thiomersal[16]. The first method, a spectrophotometric approach, used the mean centering of ratio spectra (MCR), which enhanced the signal-to-noise ratio. The second method employed reversed-phase HPLC (RP-HPLC) on a Zorbax C18 column with a mobile phase composed of phosphate buffer, acetonitrile, and triethylamine[17]. This method successfully quantified the three components in their mixture and validated the methods per International Conference on Harmonisation (ICH) guidelines. Both techniques demonstrated good accuracy, precision, and specificity[18].

A simple and rapid RP-HPLC method was designed for the simultaneous determination of lidocaine and cetrimonium bromide in the presence of pellet color corrigents. The method utilized a Beckman Ultrasphere ODS column, with a mobile phase consisting of water and acetonitrile at a ratio of 72:28. The method achieved accurate and precise separations, with UV detection at 208 nm. This approach was found suitable for the quantification of lidocaine in commercial formulations[19].

A study optimized and validated an RP-HPLC method for the simultaneous determination of hydrocortisone acetate and lidocaine in suppositories. The method used a methanol-water mobile phase (65:35 v/v), with a flow rate of 1.0 mL/min and UV detection at 250 nm. The validation of the method demonstrated its selectivity, precision, and robustness, making it an effective tool for quality control of suppository formulations[20].

A new RP-HPLC method was developed for the simultaneous determination of lidocaine and diclofenac diethylamine in a pharmaceutical gel formulation. The separation was carried out on a PrincetonSPHER 100 C18 column, using acetonitrile, potassium dihydrogen phosphate, and butane sulfonic acid sodium salt as the mobile phase[21]. The method showed excellent linearity, accuracy, and precision, with a mean recovery of 99.84% for lidocaine and 99.78% for diclofenac diethylamine. The method was also robust with respect to

changes in flow rate and mobile phase composition, making it suitable for routine analysis in pharmaceutical quality control[22].

A novel RP-HPLC method was developed for determining lidocaine in combination with beclomethasone dipropionate, clotrimazole, and chloramphenicol in ear drop formulations. The method utilized a gradient program on a C18 column, with a mobile phase consisting of a buffer and acetonitrile. The retention times for the active ingredients were optimized, and the method demonstrated good linearity and reproducibility, with high correlation coefficients. This method was validated for its accuracy, precision, and robustness, making it suitable for the routine analysis of ear drop formulations[23].

A validated, stability-indicating RP-HPLC method was developed for the simultaneous analysis of phenylephrine HCl, betamethasone valerate, and lidocaine HCl in pharmaceutical ointments[24]. The method used a C18 column with a mobile phase of phosphate buffer and acetonitrile, with UV detection at 270 nm. The method was optimized to ensure good resolution between the analytes and validated for various performance characteristics, including specificity, sensitivity, and reproducibility. The method was successfully applied to the analysis of ointment formulations containing these three active ingredients[25].

3. Materials and methods

3.1. Drugs & materials

The present work was done at CARS (Centre of Advanced Research in Sciences), Dhaka University, Bangladesh. Working standard of Lidocaine HCl was from a pharmaceutical industry, Dhaka, Bangladesh. Sample is collected from local market. HPLC grade methanol was procured from Active Fine Chemicals Ltd., Dhaka, Bangladesh. HPLC grade methanol & Milli-Q water were used for each solution preparation.

3.2. Instrument used

UV/Visible spectrophotometer**:** A double beam UV/Visible spectrophotometer, Shimadzu UV-1700 Pharma spec, Japan was employed with a pair of 1 cm quartz cells for all analytical work.

HPLC system: High Performance Liquid Chromatography system (shimadzu-UFLC Prominence), equipped with an auto sampler (Model-SIL 20ac HT) and UV-Visible detector (Model-SPD 20A) was used for analysis. The data was recorded with LC –solutions software.

Column Specification: An analytical reversed phase C-18 (ODS) column (4.6nm x 250mm; 5 um), Phenomenex, Inc was used for analysis.

3.3. Chromatographic conditions on HPLC

The chromatographic conditions on HPLC were set as follows: a C-18 (ODS) column (4.6mm x 250mm; 5µm) from Phenomenex, Inc. was used as the stationary phase. The mobile phase consisted of Solvent A, a mixture of HPLC grade methanol and Milli-Q water in a 50:50 v/v ratio, with the pH adjusted to 2.5 using 85% orthophosphoric acid, and Solvent B, which was HPLC grade acetonitrile. The solvent ratio was 50:50 (v/v) for Solvent A and Solvent B. Detection was performed at an absorption maximum (λ max) of 250 nm, with an injection volume of 20 µL. The flow rate was maintained at 1 mL/min, and the run time was set to 7 minutes. The retention time for lidocaine was 2.6 minutes, and the elution mode was isocratic.

3.4. Preparation of standard stock solutions

Lidocaine stock standard solution 100 µg/ml was prepared by dissolving 10mg of pure lidocaine in 100 ml HPLC grade methanol and dissolved properly in volumetric flask. Then 2 ml, 3 ml, 4 ml, 5 ml, 6 ml from this solution was taken in separate eppendor tube and each was leveled up to 10 ml to make concencentration

20µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml, 60 µg/ml accordingly. From these data standard curve was prepared by plotting area vs concentration.

3.5. Composition of lidocaine 2% Gel

Each gm contains 20 mg as Lidocaine Hydrochloride USP.

3.6. Preparation of sample stock solutions

50mg lidocaine 2% gel was weighed and dissolved in 50 ml HPLC grade methanol. After, it was kept for sonication for 20 minutes. Then it was filtered by using a filter paper to have final concentration 20 µg/ml. The area and retention time was measured at 250nm using UV-visible detector.

3.7. Solubility test and selection of solvent

Selection of solvent was based on solubility and stability of drug in solvent system as well as extraction of drug from its formulation. Solubility of lidocaine hydrochloride was checked respectively in 0.1M HCl, ethanol & water (1:99), methanol & water (50:50). For this purpose, individual stock solution (1mg/ml) was prepared for individual solvent system and further diluted by respective solvent to make 500 µg/ml solutions. Each solution was scanned by UV/Visible spectrophotometer over the range of 200-400 nm and individual spectrum was studied for each preparation to develop an appropriate solvent system. for carrying out further analysis. Methanol: Water (50:50 v/v) was selected as a solvent system for carrying out further analysis.

3.8. Determination of λ max

An exact weighed quantity of 10 mg standard lidocaine hydrochloride was transferred to an eppendor tube diluted using Methanol: Water (50:50) to make it final volume 10 ml. Then, the solution was further diluted to 500 µg/ml solution using same solvent. Finally, solutions were scanned in the entire UV range (200 to 400) to determine the λ max. The λ max of lidocaine hydrochloride was found to be 263nm.

3.9. Determination of retention time and area

Accurately weighed pure lidocaine hydrochloride was diluted using HPLC grade methanol as solvent and produce various concentration. The retention time and area were checked. The retention time was 2.6 min and the area was varied for its concentration.

3.10. Assay

Method was based on Quantitative equation method. Primary stock solution 100 µg/ml standard lidocaine hydrochloride was prepared by dissolving 10mg of pure lidocaine hydrochloride in 100ml HPLC grade Methanol in a 100 ml volumetric flask. Calibration curve was prepared by using different concentrations of standard Lidocaine hydrochloride solutions. Working standard solutions of 20, 30, 40, 50, 60 µg/ml was prepared from stock solution 100 µg/ml using HPLC grade methanol as solvent. The absorbance of these standard solutions was measured at 250 nm and calibration curve was plotted & studied to determine the amount of lidocaine in market preparation.

4. Results

Stock solution (1 mg/ml) of standard lidocaine hydrochloride was prepared respectively in 0.1M HCl, ethanol & water (1:99), methanol & water (50:50). Then, individual stock solution was further diluted to 500 µg/ml solution. Each solution was scanned over the range of 200-400 nm and λ_{max} was found 263 ± 1nm for individual preparation. Therefore, it was decided to use lidocaine HCl as standard solution for the total experiment. Three different working solutions for each 5, 10, 15, 20 and 25 µg/ml concentrations of

Lidocaine HCl were prepared by dilution with 0.1M HCl solvent system and absorbance were taken at 263 nm (**Table 4.1**). A calibration curve was constructed using the average absorbance values of the 5 different standard concentrations and their standard deviations were also calculated (**Figure 4.1**and **4.2**). A linear relationship (R^2 = 0.998) was obtained within the concentration range experimented.

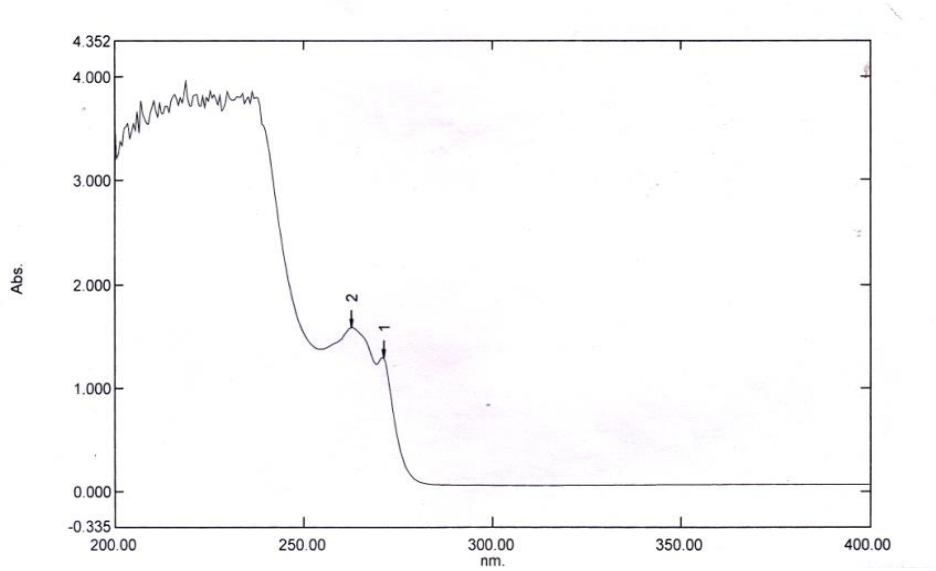

Figure 1. λ_{max} of lidocaine HCl.

Table 1. Absorbance and standard deviation (STDEV) of 5 different concentrations of standard lidocaine HCl.

Concentration (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Average Absorbance	STDEV
5	0.047	0.044	0.049	0.047	0.002517
10	0.092	0.089	0.099	0.0933	0.005132
15	0.13	0.129	0.132	0.130333	0.001528
20	0.167	0.159	0.177	0.168	0.009018
25	0.213	0.211	0.217	0.213	0.003055

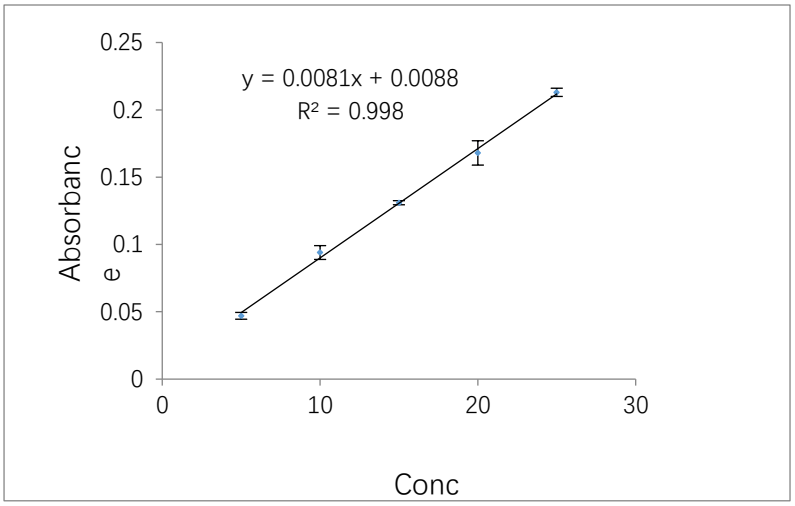

Figure 2. Calibration curve of standard lidocaine HCl.

Lidocaine HCl stock standard solution 100 µg/ml was prepared by dissolving 10mg of pure lidocaine in 100 ml HPLC grade methanol and dissolved properly in volumetric flask. Three different working solutions for each 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml, and 60 µg/ml concencentrations were prepared by dilution with the same solvent system and retention time and area were taken at 250 nm. A calibration curve was constructed using the average area values of the 5 different standard concentrations and their standard deviations were also calculated. A linear relationship (R^2 = 0.998) was obtained within the concentration range experimented. Retention time of Lidocaine HCl was 2.6 min.

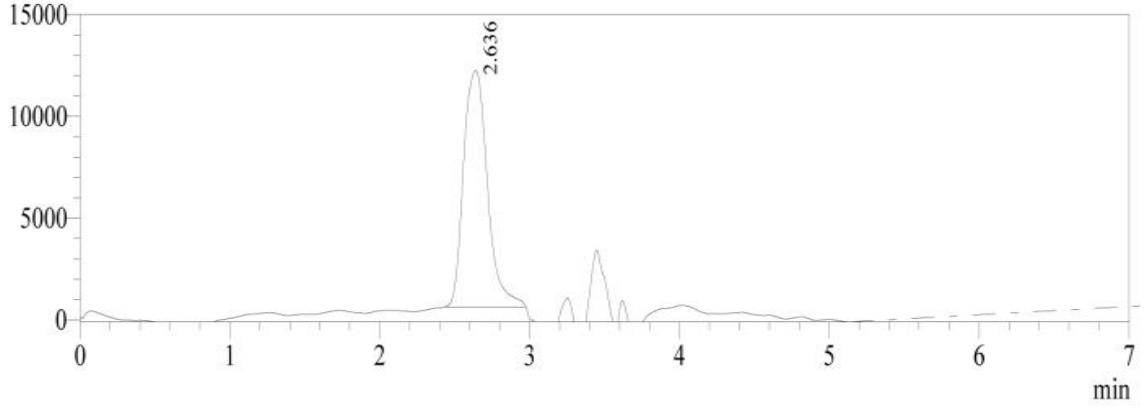

Figure 3. Retention time of standard lidocaine HCl.

Table 2. Area and standard deviation (STDEV) of 5 different concentrations of standard lidocaine HCl.

Concentration (µg/ml)	Area 01	Area 02	Area 03	Average Area	STDEV
20	35415	35267	35572	35418	152.5221
30	58175	56899	59181	58085	1143.659
40	85144	70023	85238	80135	8757.375
50	101998	101899	103744	102547	1037.814
60	129458	127960	129459	128959	865.1595

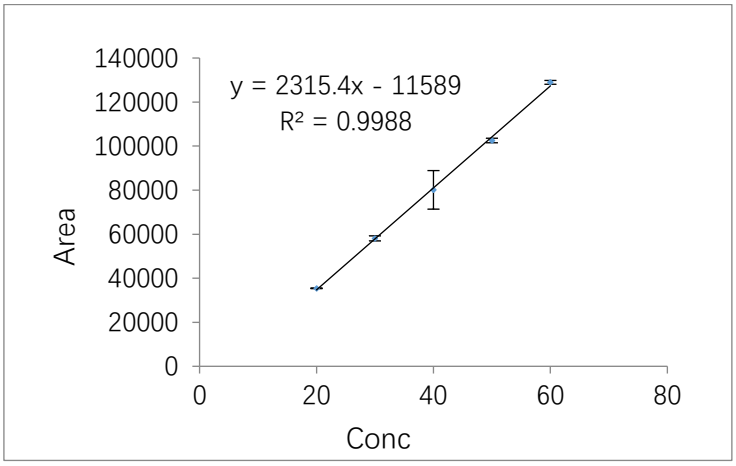

Figure 4. Calibration curve of standard lidocaine HCl.

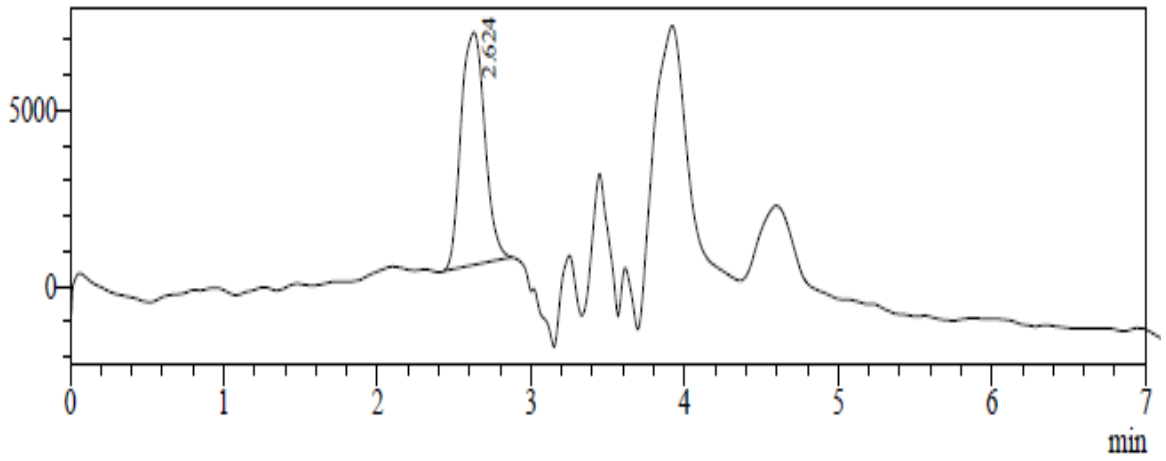

Figure 5. Chromatogram of Lidocaine HCl in sample.

Two set of working solution (20µg/ml) of sample were prepared and area, retention time was taken at 250 nm by UV-visible detector. The concentrations were calculated using the equation of calibration curve for lidocaine hydrochloride and the result is shown in **Table 4.3**.

Table 3. Area and standard deviation of sample.

Area 1	Area 2	Area 3	Conc of Area 1 (µg/ml)	Conc of Area 2 (µg/ml)	Conc of Area 3 (µg/ml)	Average of conc(µg/ml)	STDEV
71342	70767	71023	35.824	35.57	35.69	35.694	288.0746

The declared value of the lidocaine gel is that each gram contains 20 mg of Lidocaine Hydrochloride USP. However, from our analysis, it was found that each gram actually contains 35 mg of Lidocaine Hydrochloride USP. The retention time of the standard lidocaine hydrochloride was 2.6 minutes, and it was observed that the retention time of the sample was also 2.6 minutes, confirming the presence of lidocaine hydrochloride in the gel. It was noted that the market preparations of lidocaine gel contain a higher concentration of lidocaine hydrochloride than the recommended 2% by the USP, which is intended for local anesthetic effects. This discrepancy may be due to an inappropriate extraction procedure or the presence of impurities in the standard or other components used in the analysis. A higher concentration of lidocaine than the recommended range could potentially lead to elevated plasma levels, hypersensitivity, idiosyncratic reactions, or diminished tolerance in patients. However, since the gel is applied topically, it is not expected to result in significant systemic exposure.

5. Discussion

In this study, the analysis of lidocaine hydrochloride in both standard and market preparation was conducted using UV-visible spectrophotometry and High-Performance Liquid Chromatography (HPLC). Both methods were employed to determine the concentration and assess the quality of lidocaine in the gel samples.

The λ max of lidocaine hydrochloride was determined to be 263 nm, which was consistent across all three solvent systems tested: 0.1M HCl, ethanol-water (1:99), and methanol-water (50:50). This result aligns with previous studies that report a λ max of around 263 nm for lidocaine hydrochloride, confirming the

reliability of the spectrophotometric analysis for this drug. By using this wavelength, a calibration curve was constructed from standard lidocaine hydrochloride solutions. The linear regression of absorbance versus concentration yielded an excellent correlation ($R^2 = 0.998$), indicating the high precision and accuracy of the method. Similar calibration curves have been observed in other studies of lidocaine quantification using UV spectrophotometry, further validating the approach used in this study.

The retention time for the standard lidocaine hydrochloride was found to be 2.6 minutes, which was consistent with the results for the sample. The retention time being identical for both the standard and the sample suggests the presence of lidocaine hydrochloride in the gel. This aligns with previous studies of lidocaine[6], where retention times typically range from 2 to 3 minutes for similar analytical setups. The calibration curve constructed using HPLC showed a similarly high linear correlation ($R^2 = 0.998$) for the concentration range between 20-60 µg/ml, which is consistent with findings from other research where high correlation coefficients are obtained for lidocaine quantification using HPLC. The precise retention time and the linearity of the calibration curve further demonstrate the reliability of HPLC in quantifying lidocaine hydrochloride in pharmaceutical formulations.

The results of the assay for the market preparation of lidocaine gel revealed that the concentration of lidocaine hydrochloride in the gel was 35.69 µg/ml, which corresponds to 35 mg per gram of gel. This is significantly higher than the declared value of 20 mg per gram, indicating that the lidocaine concentration in the gel is higher than the recommended 2% by the USP. Several reports have noted similar deviations in market formulations, possibly due to inconsistencies in manufacturing processes, improper extraction methods, or the presence of impurities in the standard or formulation[27,28]. This higher concentration might result in unwanted side effects such as hypersensitivity, idiosyncrasy, or diminished tolerance in patients. While the topical application of lidocaine is not expected to cause systemic exposure, excessive concentration could increase the risk of side effects, particularly for individuals with sensitive skin or preexisting conditions.

A potential reason for the higher-than-expected concentration could be attributed to the gel's extraction procedure. If the extraction is not performed properly, it could lead to the presence of contaminants or an inaccurate estimation of the lidocaine content[29]. Furthermore, impurities in the standard lidocaine hydrochloride or other components in the analysis might have contributed to the discrepancy in results. This finding is consistent with the work of other researchers who noted similar challenges in accurately quantifying active pharmaceutical ingredients in complex formulations like gels and creams.

In comparison to other studies, the concentration of lidocaine found in the market gel in this study is on the higher end of the spectrum. For instance, some research found that most commercially available lidocaine gels contained concentrations closer to the 2% recommended by the USP[30]. However, deviations from this value are not uncommon, as reported in other studies, where inconsistencies were noted in the potency of lidocaine in some gel formulations[31]. Our findings suggest that, although the gel is effective, the higher concentration of lidocaine could lead to unintended adverse effects, and the formulation could benefit from a re-evaluation of its preparation method to ensure consistency and adherence to established guidelines.

6. Conclusion

A RP-HPLC method has been applied for the separation and simultaneous determination of the Lidocaine Hcl. The purpose was to develop a simple, rapid and sensitive RP-HPLC method for analysis of lidocaine in pharmaceutical dosage form. The proposed method for the determination of lidocaine hydrochloride is simple, rapid, and inexpensive and can be applied for different pharmaceutical and cosmetic products.

Conflict of interest

The authors declare no conflict of interest.

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