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An Analytical Overview of Benzoic Ester Derivative: Proparacaine

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ABSTRACT:

Proparacaine belongs to the group of medicines called local anesthetics. It belongs to the BCS class II, which are poorly water soluble. Proparacaine was first synthesized by Apothecon BV. It is found in ophthalmic solutions at a concentration of 0.5% as the hydrochloride salt. The exact mechanism whereby proparacaine and other local anesthetics influence the permeability of the cell membrane is unknown; however several studies indicate that local anesthetics may limit sodium ion permeability through the lipid layer of the nerve cell membrane. Proparacaine may alter epithelial sodium channels through interaction with channel protein residues. Examining the several analytical estimates of proparacaine and comparing it to other drug compounds is the main objective of this review. This is a comprehensive summary of earlier research on the drug proparacaine.

Keywords: Proparacaine, Local Anesthetics, HPLC, Cell Membrane.

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1. Introduction

Chemical structure formula of proparacaine is known as ($C_{16}H_{26}N_2O_3$) belongs to the class local anesthetics. Proparacaine is used for the examination of the eye or before any surgical procedure of the eye to numb the area with a pka value of 8.9, it is a white or white crystalline powder.[1-4] Proparacaine have combination with lidocaine, tetracaine, lignocaine and tropicamide. Presence of proparacaine have been reported in bulk and pharmaceutical dosage forms using various spectrophotometric methods.[5] Proparacaine stabilizes the neuronal membrane by inhibiting ionic changes necessary for the initiation and propagation of nerve action potentials. If we used proparacaine continuous then, they can result in toxic reactions to the ocular surface. Corneal stromal melting and keratopathy with the potential to result in irreversible vision loss can be led to the most concerning reaction.[6] Thus, the prolonged use of proparacaine should be avoided. Inhibition of epithelial healing causing persistent, non-healing corneal abrasions which can results in corneal scarring and edema can be include in minor toxic reactions. The adverse reactions of the drug proparacaine can include contact dermatitis, hypersensitivity reaction, burning sensation of eyes, corneal erosion, cycloplegia, eye redness, and stinging of eyes.[7]

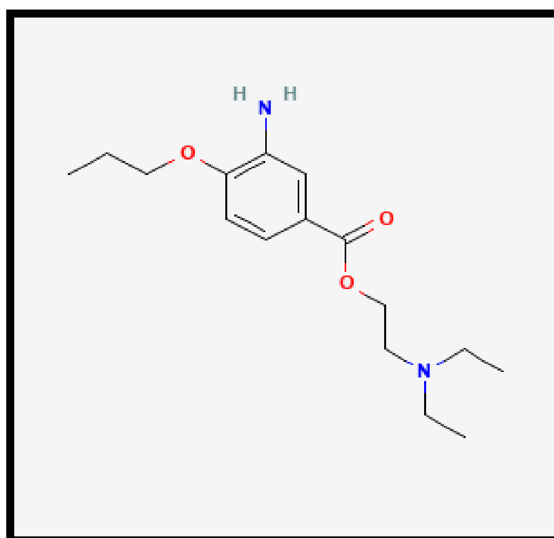

Fig 1. The composition of proparacaine chemically

Proparacaine's drug profile:
Name: Proparacaine
Molecular formula: C16H26N2O3.
Mol. Weight: 294.39 g/mol
Drug Category: local anaesthetics
Identification: Using HPLC and UV visibility
Solubility: Methanol-soluble
Physical state: White or white crystalline powder is the description.
Half-life: Ten to twenty minutes.
Medicinal Use- It is used for the examination of the eye or before any surgical procedure of the eye to numb the area.
Adverse effects- Corneal erosion, burning sensation of eyes, eye redness and cycloplegia[8-10]
Analytical Methods Description:
The associated collection of duties known as "analytical development" is where we build and measure the test procedures to support the various stages of drug development. These

procedures start with early drug development and move forward to commercial manufacture as the project changes. A strategy can be designed to guarantee the drug product's potency, identity, and purity, or to develop the characterisation and composition of the formulated drug product by following the analytical development process that determines the medication's critical quality features. Testing procedures are available for selection, and it may be shown that they follow legal criteria and are suitable for usage in all phases of the process.[11]

Creation and verification of the proparacaine RP-HPLC method:

A new, quick, easy, affordable, sensitive, and validated HPLC technique was created to detect proparacaine at an isocratic flow rate of 1 ml per minute. The C8 column was used and Methanol: orthophosphoric acid (95:5) can be used as main solvent and the wavelength can be set at 232nm. Concentration range is taken from 2-12ug/ml. The retention time of proparacaine can be 2.8min. And the LOD and LOQ was found to be 75 and 25ug/ml. The approach method was found correct, precise and straightforward. The validated method was established in compliance with ICH guidelines.[12, 13]

Concurrent formulation development and assessment of proparacaine and piracetam using RP-HPLC:

By utilizing the stability indicating RP-HPLC assay procedure proparacaine and piracetam drug can be simultaneously assessed in a dosage form. With the solvent mixture of 0.1g/L of triethylamine and acetonitrile at pH 6.1 with H3PO4 and C2H3N (90:10), isolation was achieved using an octyl carbon column. The reverse phase for proparacaine was found to be 12 minutes for CN. Using the diode array UV-Vis detector the assessment was observed at 232nm. The suggested procedure was found to be specific and linear for the simultaneous determination of the two drugs.[14]

HPTLC validation of proparacaine and citicoline sodium combined dose formulation:

For the simultaneous assessment of proparacaine and citicoline sodium as bulk and also for combination dosage form an easy and correct HPTLC procedure can be created. For the verification procedure of this process, a solvent of methanol orthophosphoric acid was utilized. Stationary phase was used is aluminum plate coated with the silica gel 60 $F_{254.}$ The densitometric analysis was carried out in absorbance mode at 240nm. The procedure was verified in concentration range of 400-2400 ng/band for proparacaine and citicoline sodium correspondingly. With the inter-day and intraday relative standard deviation, the precision procedure can be assessed. The results show that the intraday peak of the relative standard deviation of proparacaine and citicoline sodium is 1.45 and 1.07%, while the inter-day peak is 0.65 and.008%. The percentage recovery of accuracy is assessed in 3 levels. For proparacaine the outcomes is 98.55, 97.65 and 96.65% and for citicoline sodium the outcomes is 97.70, 97.75 and 97.95% correspondingly. Proparacaine and citicoline sodium spectral analysis can be used to evaluate the specification, and the standards and sample spectra can overlap accordingly.[15]

Quantitative NMR spectroscopy validation and evaluation of proparacaine in pharmaceutical:

A simple, accurate proton NMR spectroscopy (1H-NMR) method was approved to determine the proparacaine. The internal standard was deuterium oxide, while the diluent was maleic acid. Proparacaine was quantified by use of the NMR signal at 3.95 ppm and 6.30 ppm for the proton of proparacaine and deuterium oxide, respectively. Every procedure's performance, verification metrics—such as linearity—and other requirements can be satisfied. Maleic acid linearity ranges (2–12 mg/0.6 ml) and has a 0.999 correlation coefficient. Using quantitative

NMR spectroscopy, this method was the appropriate one to evaluate proparacaine in pharmaceutical dose forms and in bulk forms.[16]

RP-HPLC procedure creation as well as verification in simultaneously determining the proparacaine as well as mecobalamin as bulk and pharmaceutical dosage formulation:
A novel, quick and isocratic RP-HPLC method has been developed for the simultaneous detection of proparacaine and mecobalamin in bulk and pharmaceutical formulations Separation was accomplished using a column Phenomenex C18 with a solvent composed of pH 6.1 orthophosphoric acid buffer, C2H3N, and CH3OH in a (40:50:10) v/v/v ratio. The column oven temperature is 24°C, and the flow run is set at 1.0 ml/min and the sample cooler temperature is set at 26°c and by setting the 20L injection volume the assessment was carried out at 210nm by using photodiode array detector. The assessment of linearity for proparacaine ranges from 2-12g/ml and for mecobalamin ranges from 20.0-80.0g/ml. Proparacaine's coefficient correlation was determined to be 1.000, whereas mecobalamin's was found to be 1.002. Proparacaine had a relative standard deviation of 0.11%, while mecobalamin had a relative standard deviation of 0.03% Proparacaine has an intermediate precision of 0.78%, while mecobalamin has an intermediate precision of 0.12%. For proparacaine, the accuracy recovery rate ranged from 40 to 100%. The obtained results were determined to be limited, and the presented percentage recovered limitations are 99.01–99.74%. As a result, the identified process was successfully obtained. The percentage recovery of accuracy analysis for mecobalamin was presented at 50-120% levels. The results showed that the maximum recovery percentage was between 99.90 and 100.65%. As a result, the accuracy's procedure was verified. The process was confirmed in compliance with ICH principles. It was discovered that the described process was both consistent and reproducible.[17, 18]

Validation of RP-HPLC confirming stability in the simultaneous measurement of formulations containing citicoline and proparacaine:
For the purpose of simultaneously detecting proparacaine and citicoline in both their synthetic combination and in conjunction with their dose formulations, a robust and indicating-stability RP-HPLC method was created. By using the C18 column loaded with 10m particles, these two drugs were separated. The flow rate was set at 1.0ml/min, the solvent is in the combination containing 10 mM K_3PO_4 buffer in (90:10). The assessment for UV was performed at 232nm. The adequate linearity shows in procedure is R2=0.999 and n=3 and the of concentration for the proparacaine is 2-12g/mol and for citicoline, the concentration range is 20-40g/ml. This process was shown to be dependable even when the pH, mobile phase mix, and flow rate were purposefully changed. This approach was found to be beneficial in reliably determining the drug content of commercial pharmaceutical formulations.[19]

RP-HPLC technique development and validation of vinpocetine and proparacaine simultaneous estimation:
A validated RP-HPLC technique was created for the simultaneous detection of vinpocetine and proparacaine. The separation and analysis was carried out by using C18 column. The solvent selected is orthophosphoric acid buffer (0.05m, pH 6.0):CH_3OH (90:10 v/v), and the flow rate was set at 1.0ml/min. The wavelength was set at 225nm for analyte detection. The retention time for proparacaine is 2.08min and the retention time for vinpocetine is 7.41min was discovered. The concentration range for good linearity for proparacaine is 2-12g/mol and for vinpocetine is 80-100g/mol. The coefficient correlation of proparacaine was found to be 0.999 and for vinpocetine was found to be 0.996. For the verification of this procedure, the ICH Q2(r1) guidelines was obeyed. The percentage recovery of proparacaine was found to be 101.4 0.55% and for vinpocetine it was found to be 101.40 0.75%. It was found that the relative

standard deviation technique was precisely one, with no value greater than two. A precise, accurate, dependable, selective, and fast approach was created for the simultaneous detection of vinpocetine and proparacaine. By using the optimized methodology, the analysis of the dosage formulation was then conducted.[20]

Liquid Chromatographic quantification of proparacaine:
Proparacaine absorb maximum at 232nm. The pH of proparacaine is 4.8 and its molecular absorption is 300nm. In biological extract, direct quantification for proparacaine is difficult at 232nm. By employing chromatography of extracts using CH3OH on an isocratically produced C18 column with KH2PO4 (0.1mol/L, pH 4.9), it is possible to identify and measure 0.2 mmol of proparacaine per litre. The retention time of proparacaine was found to be 2.9min in these situations. The concentration ranges for linearity is 2-12g/mol. This procedure was suitable and quick for clinical laboratories but it is expensive.[21]

Method development for bulk and medicinal dose forms of proparacaine:
A rapid and innovative UV spectrophotometry approach was devised and validated for the measurement of proparacaine in bulk and dose formulations. In this technique, the methanol is used as a diluent. The first order derivative spectral was obtained at n=5 and the observations were taken at 232 nm with a spectral width of 2.0 nm. In the presence of formulation excipients, the method showed good linearity and excellent specificity, with concentration ranges of 2–12 g/mol. The precision data of inter and intra-day is highly reproducible. With the satisfactory outcome (mean recovery of 99.40%), accuracy was well evaluated. Proparacaine is frequently estimated using this method, which has been shown to be accurate, precise, and repeatable for both bulk and formulation forms. This procedure is validated with the aid of ICH recommendations.[22]

Using the HPLC method, proparacaine and cinnarizine dose forms were quantitatively analysed:
A new isocratic HPLC method was created for the assessment and dissociation of pharmaceutical formulations and proparacaine and cinnarizine in their purest forms. The column was utilized for separation is Hypersil hold C18 column. Calibration performed containing the range 2-12g/mol for proparacaine and 10-80g/mol for cinnarizine, the flowing run and the effects of pH and the solvent is examined. Using ICH parameters, the simultaneous determination of drugs in bulk and pharmaceuticals formulations was approved.[23]

Determination of proparacaine on newly verified GC procedure:
A verified GC procedure was developed for the assessment of the proparacaine. An internal control was implemented using tripelennamine. A nitrogen-phosphorus detector was utilized to identify proparacaine, and a fused silica capillary column was employed to separate the two. Proparacaine was prepared for gas-chromatographic analysis by means of a quick and simple liquid-phase extraction enhanced by protein removal. Parameters were found within the permissible limit range. The calibration curve's linearity ranges are 0.1 to 100g/0.5ml. Proparacaine's LOD was determined to be 0.01um/0.5ml and its LOQ to be 0.1um/0.5ml.[24,25]
Proparacaine determination method using High Performance Liquid Chromatography:
Proparacaine estimation using the current GC and HPLC methods requires large sample sizes and has interference problems. Proparacaine was determined using a micro-scale, isocratic HPLC method that made use of UV absorbance at 232 nm. Since this method did not reveal any intervention, they can be suggested as local anaesthetics. Therefore, the process may also be helpful in monitoring proparacaine use as a local anaesthetic in patents.[26]

Innovative methods for detecting cinnamon using liquid chromatography, spectro-densitometry, and spectrophotometry in conjunction with proparacaine:
For determination of proparacaine with cinnarizine in pure as well as in dosage form, unique approaches were developed and verified. The first was the densitometric analysis, which provides a rapid and simple method for measuring and separating cinnarizine. In the second step, the drug was identified using a colorimetric technique that exploits the reaction of 3-methylbenzothiazolin-2-one with an oxidant, such as FeCl3. The final product's green color, measured at 640 nm and concentrations ranging from 2 to 12 mg/ml, indicates an accuracy of 100.01 +/- 1.12 ppm. The third approach involves direct spectrophotometric measurement at 250 nm in the concentration ranges of 10–20 g/mol to identify cannarizine. By using derivative ratio spectrophotometry at 220nm in the concentration range of 10-30gm/ml, signifies proparacaine accurateness of 100.15 0.80 and 100.30 1.25% consecutively. For the estimation of proparacaine and cinnarizine by liquid chromatography, the wavelength can be set at 250nm for cinnarizine and for proparacaine can be set at 220nm, concentration ranges from 2-12mg/ml for proparacaine and 10-30mg/ml for cinnarizine, signifies accurateness of 100.05. The recommended approach was put to the test in a lab setting and was usefully used to examine their medicinal content. The simple addition method was also used to assess the strategy's performance.[27]

Validation of proparacaine or its contaminants using RP-HPLC:
Proparacaine and its contaminants such as $C_6H_9NO_3$ and $C_4H_7NO_3$ can be separated and identified by using the easy and quick HPLC method. For isolation, a C18 column was utilized. Mobile phase is consisted of the solution $(CH_2CH_3)_3$ and CH_3CN in the ratio of (85:15v/v). By adding H_3PO_4 the pH of the solvent was maintained and the flow rate is set at 1ml/min and the wavelength is set at 232nm. a method that has been found to be successful in separating pure medication from its related components. The polynomial regression data's calibration plot shows that the 45–100 ng/ml and 50–100 ng/ml concentration ranges have an acceptable linear relationship with R2=0.999. The ICH guidelines state that this procedure was confirmed. The approach is repeatable and especially helpful in estimating proparacaine and its associated elements, according to statistical estimation. This process can be used as a stability indicator because it effectively removed the medication from its related ingredients. This process is quite effective at sorting out the main ingredient.[28]

2. Conclusion

According to a literature review, proparacaine is considered as the most significant class of local anesthetics. The study's conclusion addresses the numerous analytical methods, such as UV spectrophotometry, gas chromatography, HPLC, and HPTLC.

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