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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF DALFAMPRIDINE: A REVIEW

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ABSTRACT

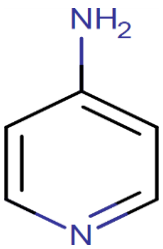
Analytical method development and validation are the continuous and inter- dependent task associated with the research and development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product specific acceptance criteria and stability of results. Validation should demonstrate that the analytical procedure is suitable for its intended purpose. Design of experiment is a powerful tool method characterization and validation. Analytical professionals should be comfortable to use it to characterize and optimize the analytical method. An effective analytical method development and its validation can provide significant improvements in precision and a reduction in bias errors. It can further help to avoid costly and time-consuming exercises. Literature survey reveals that few HPLC & HPTLC methods have been reported for the determination of Dalfampridine. The published methods were validated for various parameters as per ICH guidelines, statistical analysis provided that the published methods were reproducible and selective for the estimation of the Dalfampridine in pure and pharmaceutical dosage forms.

KEYWORDS: Dalfampridine, Validation, method development, ICH guidelines.

INTRODUCTION

Dalfampridine is a potassium channel blocker that enhances conduction in focally demyelinated axons, improves synaptic transmission, and potentiates muscle contraction. Clinically, dalfampridine has been found to improve walking in patients with multiple sclerosis. This is the first drug that was specifically approved to help with mobility in sclerosis patients. It works by strengthening the signals sent by the brain through nerves that have been damaged by multiple sclerosis. Multiple sclerosis is the most common demyelinating disease, in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to transmit signals. It is an immune-mediated disorder affecting the central nervous system.[1-3]

STRUCTURE



4-aminopyridine

Dalfampridine is chemically known as 4-aminopyridine, with a molecular formula of $C_5H_6N_2$ and a molecular weight of 94.1146 g/mol. Dalfampridine is a white crystalline powder, and it is soluble in polar solvents such as water, methanol, ethanol, and acetonitrile and consisting of a dose range of 10mg. It was found slightly soluble in ligroin. Dalfampridine is considered a broad-spectrum in action. Pharmacologically, the drug is a potassium channel blocker and mostly lipophilic in nature, which binds favourably to the open state potassium channel in the central nervous system. Dalfampridine is rapidly and completely absorbed orally to attain relative bioavailability up to 96%. The excretion takes in unchanged form, mostly from urine (96%).

REVIEW OF LITERATURE

1. **Madhumathi CH[6] et al., (2014),** developed a simple, accurate, precise, reproducible, sensitive, economic, spectrophotometric method for the quantitative estimation of Dalfampridine in tablet dosage form. The method was developed based on the solubility of dalfampridine in water. The developed method was validated with linearity, accuracy, and precision. The drug showed maximum absorbance at 247 nm. Linearity was obeyed in the concentration range of 2–10µg/ml. The results of the analysis were validated statistically.

2. **Vivek Kumar Redasani K.[7] et al., (2014),** developed simple, precise, and cost-effective spectrophotometric methods (four methods) for the estimation of dalfampridine in bulk and its tablet formulation. Dalfampridine was estimated at 262nm in UV spectroscopy (method A), 274.5nm in first-order derivative spectroscopy (method B), scanned at 254.2–269.0 nm in area under curve for zero-order derivative spectroscopy (method C), and at 267.2–284.2 nm in area under curve for first-order derivative spectroscopy (method D). The drug follows Beer-Lamberts law in the concentration range of 2.0–7.0µg/mL for all the methods. The developed methods were successfully applied to estimate the amount of dalfampridine in bulk and in tablet formulations.
3. **Khadiga Kelani M.[8] et al., (2023),** described three spectrophotometric techniques that were developed and verified for the reliable identification of Dalfampridine (DFP) in the presence of its oxidative derivative, namely derivative ratio DD, ratio subtraction RD, and bivariate BI. Linearity was established in the range of 1–14 ug/ml. The established techniques have been effectively used to analyse Dalfampridine (DFP) in its pharmaceutical dosage form. The degradation pathway was confirmed by using TLC, IR, 1H NMR, and mass spectrometry. In addition to the analytical greenness metrics (AGREE) method, analytical eco-scale tools were applied to DFP with greenness assessment.
4. **EL-Fatatry HM[9] et al., (2013),** A sensitive, simple, and selective spectrofluorimetric method was developed for the determination of dalfampridine. The developed method was based on the reaction between the drug and fluorescamine in a borate buffer of pH 8.5 to give a highly fluorescent derivative that was measured at 485 nm using an excitation wavelength of 385 nm. The optimum reaction conditions were determined by the factorial design of the experiment, and the method was applied for the determination of Dalfampridine over the concentration range of 20–100ng/ml. The suggested method was successfully applied to a synthetic mixture simulated in tablet dosage form. The mean recovery from the synthetic mixture was found to be 98.89% ± 1.17 with no interference from excipients.
5. **Vivek Jain[10] et al., (2019)**, developed an accurate, precise, and reproducible UV spectrophotometric and liquid chromatographic assay method for the determination of Dalfampridine in synthetic mixture form. Spectrophotometric estimation was done by the calibration curve method using 0.1N NaOH as a solvent. In this method, the λmax for Dalfampridine was 244 nm. The RP-HPLC method was developed by the isocratic technique on a reversed-phase thermos-column C18 (250×4.6 mm, 5µm) with methanol and acetonitrile (50:50 v/v) as a mobile phase at a flow rate of 1.0 ml/min. The retention time for Dalfampridine was 4.186 + 0.3 min. The linearity range of Dalfampridine was 5–25µg/mL for both the HPLC and UV methods. The method showed good reproducibility and recovery, with relative standard deviations less than 2%.
6. **Rathod KG[11] et al., (2019),** developed A rapid and precise reverse-phase high-performance liquid chromatographic method for the validation of Dalfampridine in its pure form as well as in tablet dosage form. Chromatography was carried out on an ODS C18 (4.6 x 250mm, 5µm) column using acetonitrile and water (80:20v/v) used as a mobile phase at a flow rate of 1.0 mL/min. The retention time obtained for DFP was found to be 2.98 minutes. The method produces linear responses and a RSD less than 2. The method is useful in the quality control of bulk and pharmaceutical dosage forms.
7. **Prashanthi T.[12] et al., (2019),** developed a simple, precise, rapid, and accurate reverse-phase high-performance liquid chromatographic method for the estimation of Dalfampridine in bulk and tablet dosage form. The separation of Dalfampridine was achieved by a Phenomenex C18 column (125 × 4.6mm, 5µm) by using sodium acetate pH 4.5 and methanol (60:40 v/v) as a mobile phase at a flow rate of 0.8 ml/min. Dalfampridine was eluted at 1.713 min. Linearity in the method was measured in the concentration range of 5–25µg/ml, and the LOD and LOQ were found to be 0.107µg/ml and 0.323µg/ml, respectively. Acid, alkali, oxidative, thermal, and neutral degradation studies were performed. Hence, this method can be routinely applicable for analyses of Dalfampridine in pure and tablet dosage forms.
8. **Bagal[13] et al., (2021),** developed a simple, improved, precise, rapid, and accurate RP-HPLC method for the estimation of Dalfampridine in bulk and tablet dosage form. This separation of dalfampridine was achieved isocratically on a C18 column (250x4.6mm, 5µg) using (0.1v/v) buffer pH 3.0 ± 0.05 adjusted with diluted ortho-phosphoric acid and acetonitrile in the ratio of 60:40 (v/v) as a mobile phase at a flow rate of 0.5ml/min and column temperature of 40˚c. HPLC-grade methanol was used as a diluent, 5µl of standard solution drug was injected, and the eluted analyte were detected at 262nm. Dalfampridine was eluted at 4.5 min with a run time of 10 min. Dalfampridine was subjected to a forced degradation stability study in conditions of thermal, acid, alkali, and oxidation and Photo-degradation condition.
9. **Dharani NR[14] et al., (2016), A** stability-indicating reverse-phase high-performance liquid chromatographic (Inertsil-C18 column) method has been developed and validated for the estimation of Dalfampridine in its bulk and formulation. The chromatographic separation was achieved by using acetonitrile and potassium dihydrogen phosphate buffer (pH was adjusted to 4 with orthophosphoric acid) in the ratio of 70:30v/v as a mobile phase and a flow rate of 1.0ml/min. The linearity was observed

from 20 to 80 µg/ml with a correlation coefficient of 0.999. The chromatographic retention time of the proposed method was 2.43 min. For the stability study, the drug was exposed to stress conditions such as acid, alkaline, oxidation, and thermal by using 0.1M HCl, 0.1M NaOH, and 30% H2O2 at 100 °C. Degradation behaviour shows that the major degradation was observed at acidic conditions (80.11%), followed by thermal (70.25%), alkaline (67.12%), and oxidation (63.42%). The proposed method was successfully applied for the quantitative determination of dalfampridine in bulk and pharmaceutical formulations. The relative standard deviations for linearity and precision did not exceed 2%.

10. **Gopinadh Vuyyala[15] et al., (2023),** A basic, specific LC strategy is portrayed for the assurance of Dalfampridine tablet measurement structures. Chromatographic partition was accomplished on a C18 section utilizing a portable stage comprising a combination of mixed phosphate cradle pH 3.5. and acetonitrile (30:70v/v) with a discovery of 244nm. The linearity was seen in the range of 35–105µg/ml, and the correlation coefficient was found to be 0.998. A few scientific strategies have been proposed for the quantitative assessment of Dalfampridine independently and in combination with different medications. So, endeavor was taken to create and approve a switched-stage superior execution fluid chromatographic technique for the quality control of Dalfampridine in drug arrangements with lower dissolvable utilization alongside the short logical run time that prompts a harmless to the ecosystem chromatographic system.

CONCLUSION

Literature survey suggested that various HPLC, UV and few HPTLC methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of the Dalfampridine in pure and pharmaceutical dosage form.

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