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Physico-Chemical Characterization and Analytical Development for Sodium Azumolene, a Potential Drug Designed to Fight Malignant Hyperthermia

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Introduction:
Sodium azumolene is a drug designed to fight Malignant Hyperthermia (MH), which is characterized by genetic predisposition and triggered by the use of inhalational anesthetics. This drug is shown as a water-soluble analogue of dantrolene sodium, 30-folds more water soluble, which gives advantages for its emergency use. To our knowledge there is no analytical method for sodium zaumolene raw material or dosage form published so far. The objective of the present investigation was to develop and validate analytical methods to achieve sodium azumolene chemical identification and quantification. The sodium azumolene was characterized regarding its thermal behavior, by differential thermal analysis and thermogravimetric analysis; Visible, UV and infrared absorption. To accurately assess the sodium Azumolene content three different analytical methods (visible and UV spectrophotometry and high performance liquid chromatography) were developed and validated. All methods showed to be linear, accurate, precise and reliable. Azumolene has shown to be equipotent to dantrolene in the treatment and prevention of an MH crisis and the great advantage compared to dantrolene is better water solubility. This study has characterized the sodium azumolene and presents new analytical methods which have not been reported so far.

Objectives:
All LC, UV and VIS spectrophotometric methods were validated according to the International Conference on Harmonization (ICH) guidelines. The following characteristics were considered for validation: Linearity, range, accuracy and precision. Linearity was determined in the range 5.0 to 15.0 µg/mL (LC method); 7.0to 12.0 µg/mL (UV spectrophotometric method) and 8.0 to 13.0 µg/mL (Vis spectrophotometric method). The least squared method was used to calculate the regression coefficient from peak area or absorption vs. concentration of standard solutions. Accuracy was tested by calculating the percentage recoveries of sodium azumolene from sample solutions at different concentrations and by determining the relative standard deviation (RSD). Precision was assessed at different levels–repeatability (system repeatability by testing three curves constructed with five different standard solution concentrations, in the same day); and intermediate (by analyzing three different standard solution concentrations high, intermediate and low, in a different day, with two days interval between repeatability and intermediate).
The limits of detection (LOD) and quantification (LOQ) were calculated as 3 and 10 σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of y-intercept of regression equation.

Results:
Plant-derived polymers have found specific applications in drug
The LC method validated is fast (retention time=4.25 min) and optimized method. Good symmetry was obtained by using endcapped column (C18 4.6×250 mm; 5 µm) and mix of methanol and water (75:25, v/v, pH 3.0 adjust with formic acid) as mobile phase. Good linearity was obtained at the concentration range tested. It was evaluated by the analysis of variance (ANOVA) and results showed regression statistically significant (Fcalculated<Fcritical; P=0.05). The equation of the curve was y=44299X+137924 with a good coefficient of determination (r2=0.9990). The precision of the method was determined by repeatability (intra-day) and intermediate precision (inter-day) and was expressed as R.S.D. (%) of a series of measurement. The repeatability test shows R.S.D. equal to 0.08 and the inter-day variability was equal to 1.23%. The accuracy of the method was determined by the mean recovery, by adding standard to sample. The mean result was 98.14 % indicating an agreement between the true value and the value found. LOD and LOQ were determined based on the standard deviation of the response and the slope, based on the calibration curve and the values were 0.95 and 2.89 µg/mL, respectively. To evaluate the robustness of the proposed method low and deliberate changes were made on the flux rate of mobile phase. Sample and standard solutions were submitted at the following flux rate 0.9; 1.0 and 1.1 mL/min. No interference over assay test was found. All validated methods showed to be precise, accurate and linear at the concentration ranges tested. The chromatographic method is the most expensive method, since it requires special equipment and expensive solvents. The UV-VIS spectrophotometric methods are easier, more economical and faster than the LC method, however the LC-method is more precise and can readily identify interfering peaks.

Conclusion:
For routine quality control of medicines, it is essential to employ well-characterized, fully validated analytical methods to obtain reliable results that can be satisfactorily interpreted. The proposed methods were used successfully to investigate the sodium azumolene content. All methods are simple and efficient; and they were validated showing accurate and excellent linearity and precision characteristics. Our study leads to conclude that the three validated method can be used to determine sodium azumolene and applied as quality control tools. The choice of the method to use should be made considering cost, simplicity, equipment, solvents, speed, and application to large or small workloads.