

APPROACHES TO THE SELECTION OF THE OPTIMAL MOBILE PHASES IN THE DEVELOPMENT OF HPLC METHOD FOR THE DETERMINATION OF MELDONIUM IN DOSAGE FORMS

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Introduction. Meldonium (Mildronate) is a metabolic, cardioprotective drug, a structural analogue of gammabutyrobethaine (precursor of carnitine), which is used for the treatment of cardiovascular complications and for improving the functioning of the brain. Chemical name meldonium dehydrate is 3-(2,2,2-trimethylhydrazin-2-ium-1-yl)propanoate dihydrate, is water soluble molecule (20.2 mg/mL) with log P= -2.6, pKa (strongest acidic)= 4.14 . There were only one spectrophotometric and three chromatographic methods determination of meldonium in dosage forms. Due to the toxicity of the reagents and outdated methods of analysis, the use of these methods is impractical. Investigations and experiments of salts for chaotropic anions are quite new and promising in the development of HPLC methods. Therefore, **the aim** of our work was to create an approaches to the selection of the optimal mobile phases in the development of HPLC method for the determination of meldonium in dosage forms.

Materials and methods. Analytical equipment: Shimadzu UPLC system LC-40 PDA; Shimadzu Nexera-i LC-2040C 3D-Plus, controlled by software Lab Solution version 5.97, laboratory electronic balance RAD WAG AS 200/C, pH-meter И-160ММ. Meldonium dihydrate (purity 99.3 %) was purchased from Sigma-Aldrich (Switzerland), Vasopro capsules 500 mg was purchased from local pharmacy. Chromatographic conditions: Agilent Zorbax C-18 SB 150 mm x 4.6 mm 3.5 μm column was used (Agilent Technologies, USA). Mobile phases: 1) 0.25% KPF6 w/v – 0.1% v/v 85% H₃PO₄ 95% – 5% ACN, 2) 0.3% bis-(trifluoromethane)sulfonimide lithium salt 97% w/v – 0.1% v/v 85% H₃PO₄ 80% – 20% acetonitrile. Flow rate - 1 mL/min, T=32 °C, detection UV at 4 channels - 190 nm, 195 nm, 200 nm, 205 nm.

Results and discussion. We have proposed two approaches using two different salts of chaotropic anions - potassium hexafluorophosphate and bis-(trifluoromethane)sulfonimide lithium salt – for the HPLC method development. The chaotropic effects of these anions toward meldonium strongly influenced the analyte migratory behavior. Both mobile phases involved, in addition to the use of a chaotrope, also the use of acetonitrile and pH adjustment with 0.1% v/v 85% H₃PO₄ solution. The detection wavelength (190 nm, 195 nm, 200 nm, 205 nm) was selected experimentally. The results were obtained for 8 concepts. Parameters of the chromatographic system confirm the conclusions and results of this investigation for the influence of chaotropic salts on N-containing molecule in acidic pH medium, by increasing their retentivity, and improving peak shape and uniformity homogeneity, even on column without end-capping and base-deactivating.

Conclusions. HPLC method for the determination of meldonium in dosage forms has been developed, with using positive impacts of chaotropic salts on the molecules containing N-atoms in their molecule on their retentions and peak symmetries on the chromatogram.