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Short communication

Development and validation of ICP-OES method for determination of elemental impurities in some opiate alkaloids

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Introduction

One of the biggest challenges in the pharmaceutical industry is determination of elemental impurities in drugs. The most important goal is to obtain their qualitative and quantitative presence, considering the reasons that may explain their occurrence. The target molecules in this work are represented by some important opium alkaloids (European Medicines Agency, Q3D, 2019). Alkaloids are naturally occurring organic nitrogen-containing bases with heterocyclic structure which are isolated from the opium poppy, also known as *Papaver somniferum*. Their final pharmaceutical formulations (tablets, syrups and injections) are intended for treatment of illnesses in children's and adults and their detailed analysis in terms of elemental impurities is especially important (Bribi et al., 2018).

Therefore, the aim of this work was to develop simple and effective method for determination of elemental impurities in three types of related opium alkaloids: pholcodine monohydrate, codeine phosphate sesquihydrate and morphine (as hydrochloride and sulphate form) by using a common atomic spectroscopy technique by means of inductively coupled plasma – optical emission spectroscopy (ICP-OES). The technique is often used in all modern industrial laboratories because of its specificity, precision, economy and most importantly – its accuracy (Barin, 2016).

The developed ICP-OES method was validated in accordance to the requirements for validation of methods prescribed by the European pharmacopoeia and the ICH – Q3D guideline. Furthermore, the same validated method can be used even in conditions of an altered synthesis of the alkaloids discussed.

Materials and methods

Materials

Ultrapure water with a resistivity of 15 MΩ used in the validation was prepared by passing water through a Milli-Q Type Ultra-pure water system (EMD Millipore, Billerica, MA, USA); concentrated nitric acid (70%, v/v, trace metal grade) and hydrochloride acid (37%, v/v, trace metal grade), both purchased from Sigma Aldrich (St. Louis, MO, USA). Standard solutions for calibration and spike solutions for recovery assessment were prepared by diluting commercially available Multi Analyte Custom Grade Solution (containing 24 elements according to ICH Q3D concentrations) purchased by Inorganic Ventures (Christiansburg, Virginia, USA) and test samples (three batches from each analyzed alkaloid) were provided from Alkaloid AD, Skopje, Republic of North Macedonia.

Microwave digestion method and sample preparation

EthosUP microwave digestion system employing SK-15 digestion vessels was used for sample digestion. 0.55 g of each alkaloid mentioned above were carefully weighed into a microwave vessel followed by addition of 5 mL of ultrapure water; 3 mL nitric acid and 2 mL of hydrochloride acid. A microwave digestion program utilizes a two-step microwave program consisting of a 20 min ramp time to 210ºC with a hold time of 15 min on 210ºC at 1800 W power. Digested samples were transferred into 25 mL volumetric flasks and diluted to the final volume of 25 mL with ultrapure water.

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ICP-OES method

The analysis was performed on Agilent 5100 ICP-OES VDV system coupled with Agilent SPS-4 autosampler. The instrument parameters were the follows: RF power: 1.40 kW; Plasma Ar flow rate: 14 L min^{-1}; Auxiliary Ar flow rate: 1.0 L min^{-1}; Pneumatic Nebulizer Ar flow rate: 0.70 L min^{-1}; Pump speed: 12 rpm; Viewing mode: Axial; Number of replicates: 5; Background correction: Fitted.

Results and discussion

Validation was made in accordance with the ICH Q2(R1) topic – "Validation of Analytical procedures: Text and Methodology" (European Medicines Agency Q2, 1995). Opiate alkaloids were tested for the presence of elemental impurities from Class 1; Class 2a; Class 2b and Class 3. Having in mind that these active pharmaceutical ingredients exhibit different type of formulation and whose daily intake is unspecified, the maximum permitted concentration (µg/g) was calculated as per option 1 from the ICH Q3D guideline. The quantitative method was validated for system suitability, specificity, linearity, precision, accuracy, limit of detection (LOD) and limit of quantification (LOQ). System suitability was demonstrated with the microwave digestion by obtaining clear and colorless samples and difference between two measurement of the standard less than 20%. Specificity was confirmed by presence of the signal from each element in the standard sample and its absence in the blank. By achieving correlation coefficient of more than 0.99 for each element of interest, the parameter linearity was obtained. Precision was proven by: system precision - six consistently repeated measurements from one sample and method precision - six individually spiked samples at 100% concentration level. The obtained results indicate good precision or less than 20% relative standard deviation. Method accuracy was demonstrated by the recovery of a known amounts of the elements spiked into the substances, prior to digestion procedure. Each was spiked on 50%; 100% and 150% specification level and the spike recoveries were satisfactory between 70% and 150% for each element. Limit of detection (not more than 0.5 times from the concentration of the specification level) and limit of quantification (bellow the specification limit) were satisfied and performed using signal-to-background ratio and the relative standard deviation of the signal background (three times the standard deviation of the background for the blank for LOD and ten times for the LOQ).

Conclusion

Regular control of elemental impurities in the pharmaceuticals and their preparations is the main step towards obtaining a quality and safe drug product. The presented ICP-OES method covering the determination of 24 elements (Class 1; Class 2a; Class 2b and Class 3) was successively validated following the ICH Q2(R1) directions. The method for the determination of elemental impurities in these active opiate alkaloids has been shown to be selective and specific in order to qualify and quantify trace elements. This validated analytical method was tested on real samples of each opiate alkaloid. The developed method has proven that the 24 analyzed elements do not exceed 30% of the specific level, which means that each of the analyzed active ingredient is safe for admission in the final drug product.

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