STUDY OF UNKNOWN IMPURITIES IN MEDICINES: AN EXAMPLE OF TIES BETWEEN THE PRODUCTION SECTOR AND ACADEMIA

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ABSTRACT

The present work addresses the categorization of organic impurities in medications, as well as discusses the identification, isolation, and characterization of unknown degradation products observed during stability and forced degradation studies. The entire approach aims at defining an appropriate specification and analyzing the impurity, enabling a comprehensive understanding of the product, which is an indispensable object during the registration process with the National Health Surveillance Agency (ANVISA). In light of this, this study is the result of technical-scientific cooperation between the productive sector and academia, in the search to identify, isolate, and characterize an unknown impurity found in one of the proton pump inhibitor medications from a pharmaceutical industry.

Keywords: impurities; stability; identification; characterization.

INTRODUCTION

It is defined that an impurity within the pharmaceutical scope is any component present in the pharmaceutical input or the finished product that is neither the active pharmaceutical ingredient nor the excipient(s) (RDC 53, 2019). This can originate from various sources, namely: organic, inorganic, and residual solvents. Organic impurities can be attributed to those that may arise during the manufacturing and/or storage process of a drug, for example: starting material; by-product; intermediate; degradation product; reagents, ligands, and catalysts (ICH Q3A (R2), 2006).

In the context of regulation, the Collegiate Board Resolution (RDC) No. 53 of December 4, 2015 "establishes parameters for the notification, identification, and qualification of degradation products in medicines with synthetic and semisynthetic

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active substances, classified as new, generic, and similar, and provides other measures." Article 9 of this resolution brings the need for identification of the degradation product in cases where the identification limits are exceeded.

For the identification, isolation, and characterization of degradation impurities, a combination of various spectrophotometric techniques such as chromatography, mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, infrared spectrometry, among others, are used (Qiu & Norwood, 2007). This diversity of techniques is necessary since degradation impurities can be present in complex mixtures and at low concentrations. Therefore, the methods for these analyses need to be capable of separating, identifying, and quantifying chemical compounds with high sensitivity and specificity.

Finally, impurities referred to as unknown, that is, those whose structure has not been elucidated, must be controlled below the identification limit. As for impurities with a known structure and no structural alerts, they should be controlled below the qualification limit, and impurities with a known structure and structural alerts should have their limits established after a toxicological study (ICH Q3B (R2), 2006). However, it is worth noting that this structuring should not be general, therefore, other references should still be considered, such as specifications described in official compendiums. Based on these guidelines, the present study aims to promote the identification, purification, and characterization of an unknown impurity found in one of the medications of a pharmaceutical industry.

METHODOLOGY

The drug/pharmaceutical object of this study was subjected to a long-term stability study in accordance with the guidelines established in RDC 318 of November 6, 2019. An analytical method was developed and validated according to the guidelines of RDC 53/2015, Guide 04/2015, and RDC 166/2017, and the study impurity was observed using high-performance liquid chromatography (HPLC).

RESULTS

The high-performance liquid chromatography separation technique is based on the interaction between the mobile phase and the stationary phase, which, considering the polarity of the molecules under study, are eluted at different retention times. Having an adequate separation, that is, a methodology that contains satisfactory specificity and considering that it possesses precision and accuracy, it is possible to guarantee the quantification of any substance present in the drug under study.

In this sense, within the scope of the experimental work carried out, the development and validation of an analytical methodology for HPLC was initiated. Subsequently, aiming at the quantification of impurities in the finished product, the previously developed analytical methodology was applied for the analysis of the medication. From the analysis of the obtained results, an unknown organic impurity close to the limit recommended by ANVISA was observed. Therefore, a preparative chromatography separation methodology is currently under development and will be applied for the purification of the previously observed organic impurity.

CONCLUSION

The drug under study, which is part of the class of proton pump inhibitors, contains a non-specific organic impurity that was identified through chromatography techniques. In this sense, as future perspectives, the identified organic impurity will be quantified, isolated, and adequately characterized, ensuring the real identification of the molecule and consequently the definition of a new specification for the now-known impurity. All this approach supports the product development aimed at the registration of the drug with ANVISA.

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