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Application of Analytical Quality by Design concept for bilastine and its degradation impurities determination by hydrophilic interaction liquid chromatographic method

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ABSTRACT

This paper deals with the development of hydrophilic interaction liquid chromatographic (HILIC) method for the analysis of bilastine and its degradation impurities following Analytical Quality by Design approach. It is the first time that the method for bilastine and its impurities is proposed. The main objective was to identify the conditions where an adequate separation in minimal analysis duration could be achieved within a robust region. Critical process parameters which have the most influence on method performance were defined as acetonitrile content in the mobile phase, pH of the aqueous phase and ammonium acetate concentration in the aqueous phase. Box-Behnken design was applied for establishing a relationship between critical process parameters and critical quality attributes. The defined mathematical models and Monte Carlo simulations were used to identify the design space. Fractional factorial design was applied for experimental robustness testing and the method is validated to verify the adequacy of selected optimal conditions: the analytical column Luna® HILIC (100 mm × 4.6 mm, 5 μm particle size); mobile phase consisted of acetonitrile—aqueous phase (50 mM ammonium acetate, pH adjusted to 5.3 with glacial acetic acid) (90.5:9.5, v/v); column temperature 30 °C, mobile phase flow rate 1 mL min^{-1}, wavelength of detection 275 nm.

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1. Introduction

Bilastine, 2-[4-(2-(4-(1-(2-ethoxyethyl)-1H-benzimidazol-2-yl)piperidin-1-yl)ethyl)phenyl]-2-methylpropionic acid, is a novel second-generation H_1 antihistamine, which has not shown sedative or cardiotoxic effects in clinical trials and in post-marketing experience so far. It is developed for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria [1]. Bilastine has recently been granted marketing authorization in most European countries in form of solid unit-dose preparations (tablets) with a 20 mg per unit dose. The approved dose is 20 mg once a day for the relief of symptoms of allergic rhinoconjunctivitis and urticaria.

Bilastine is a non-compendial substance, so there are not yet compendial methods for the assay or impurities determination to be found in The European Pharmacopoeia or national pharmacopoeias. There are no published papers found by literature review dealing with development of analytical methods for bilastine testing in dosage forms, but there are some published papers dealing with the efficacy, safety and pharmacokinetics of bilastine and its determination in biological samples [1–5].

Structures of investigated substances are presented in Fig. 1.

Bilastine is non-chiral molecule, with molecular formula $C_{28}H_{37}N_3O_3$ and molecular weight 463.1 g/mol. Chemical names of investigated degradation impurities are:

Impurity 1—Cis-2-[4-(2-{4-[1-(2-Ethoxy-ethyl)-1H-benzoimidazol-2-yl]-1-oxy-piperidin-1-yl}-ethyl)-phenyl]-2-methylpropionic acid

Impurity 2—Trans-2-[4-(2-{4-[1-(2-Ethoxy-ethyl)-1H-benzoimidazol-2-yl]-1-oxy-piperidin-1-yl}-ethyl)-phenyl]-2-methylpropionic acid

The aim of this paper is to develop a specific and robust hydrophilic interaction liquid chromatographic (HILIC) method for the analysis of bilastine and its degradation impurities with minimal duration time following Analytical Quality by Design (AQbD) approach. HILIC is a very complex and non-robust technique, so the application of AQbD is of great importance. Literature review showed that only one paper, published by our research group, applied the QbD concept in development of HILIC method [6].

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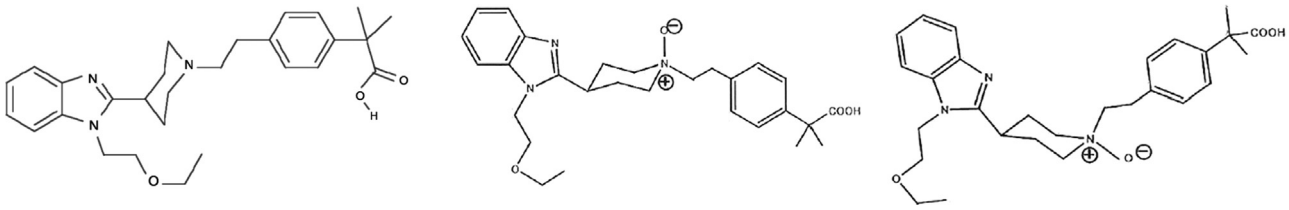

Fig. 1. The chemical structures of investigated substances.

HILIC is a relatively young analytical technique used for the analysis of small polar analytes, which is becoming as important as reversed phase liquid chromatography (RP-LC). Having in mind that investigated substances are charged at wide range of pH, HILIC was chosen for their separation. HILIC can be characterized as the chromatographic technique using NP stationary phase in combination with RP mobile phase, containing more than 50% organic solvent in water. It often provides sufficient retention of strongly polar compounds, for which it offers different selectivity compared to the traditional RP chromatography [7,8]. In HILIC, elution conditions have more influence on retention then the ones observed in RP-LC and it involves more complex retention mechanisms. The most important parameters that influence the retention behavior of the analytes are organic solvent content, pH and salt concentration. Acetonitrile is the most used solvent for HILIC separations. The other component of the mobile phase is water or aqueous buffer. The aqueous buffer content must be at least 3% to create a water layer on the surface of the stationary phase. Salts are usually added to water for controlling electrostatic interactions between charged analytes and the stationary phase, to improve peak shape and to reduce peak tailing.

Quality by Design (QbD) is defined according to The International Conference on Harmonization quality guideline Q8 (ICH Q8(R2)) as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [9]. ICH Q9 [10] and ICH Q10 [11] guidelines are also dealing with QbD concept which entails building quality into the process and the product instead of testing it. Increasing adoption of QbD approaches to process development is equally desirable with respect to analytical controls. One of the QbD objectives in analytical chemistry is to better understand the influence of the critical process parameters (CPPs) on the critical quality attributes (CQAs) chosen for the method. The incorporation of AQbD strategy in the HILIC method is very useful since it is a complex type of chromatography and enables dealing with optimization challenges in controlled manner, especially when developing a method for the analytes that have never been investigated before. Therefore, it is important to have a systematic approach which would lead to the best possible results.

2. Materials and methods

2.1. Chemicals and reagents

All the reagents utilized in this study were of the analytical grade. The mobile phase and the solvents were prepared from acetonitrile (*Avantor Performance Materials BV*, Deventer, Netherlands), methanol (*Sigma-Aldrich Co.*, St. Louis, MO, USA), ammonium acetate (*Riedel-de Haën*, *Sigma-Aldrich Laborchemikalien GmbH*, Seelze, Germany), glacial acetic acid (*Zorka Pharma*, Šabac, Serbia) and HPLC grade water. Nixar® 20 mg tablets were obtained from the local pharmaceutical market.

2.2. Chromatographic conditions

The chromatographic system Waters Breeze consisted of Waters 1525 Binary HPLC Pump, Waters 2487 UV-vis spectroscopy dual absorbance detector and Empower 2 Software. Separations were performed on Luna® HILIC column 100 mm × 4.6 mm, 5 μm particle size (Phenomenex Technologies, Torrance, CA, USA). The samples were introduced through a Rheodyne injector valve with a 20 μL sample loop. Throughout the whole experimental procedure the following instrumental chromatographic conditions were maintained: flow rate of the mobile phase 1 mL min^{-1} and column temperature 30 °C, ultraviolet detection at 275 nm.

2.3. Mobile phase

Mobile phase consisted of acetonitrile and aqueous phase (with added ammonium acetate and glacial acetic acid) where the amount of organic solvent, ammonium acetate concentration in the aqueous phase and pH of the aqueous phase were varied according to the experimental plan. Mobile phase under optimal chromatographic conditions was as follows: acetonitrile – 50 mmol L^{-1} ammonium acetate in water adjusted with glacial acetic acid to pH 5.3 (90.5:9.5, v/v).

2.4. Standard solutions

2.4.1. Solutions for the method optimization and robustness testing

First stock solutions were prepared by dissolving 1 mg of bilastine and its impurities in 10 mL of methanol. The concentration of the first stock solutions was 100 μg mL^{-1}. In order to obtain

Table 1
Plan of experiments and the obtained results for CQAs.

Exp.	x_1	x_2	x_3	k_3	α2
1	90	40	4.75	3.53	1.50
2	94	40	4.75	23.65	1.65
3	90	80	4.75	3.47	1.38
4	94	80	4.75	20.19	1.5
5	90	60	4.0	1.34	1.26
6	94	60	4.0	8.78	1.36
7	90	60	5.5	4.24	1.43
8	94	60	5.5	28.96	1.64
9	92	40	4.0	3.63	1.33
10	92	80	4.0	2.90	1.23
11	92	40	5.5	9.92	1.72
12	92	80	5.5	10.53	1.61
13	92	60	4.75	7.34	1.47
14	92	60	4.75	7.08	1.46
15	92	60	4.75	7.86	1.51

Exp.—number of experiment; x_1—acetonitrile content in the mobile phase (%); x_2—ammonium acetate concentration in the aqueous phase (mmol L^{-1}); x_3—pH of the aqueous phase; k_3—retention factor of *Impurity 2*; α_2—selectivity factor of critical peak pair (*Impurity 1* and *Impurity 2*).

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