Quantitative analysis of 3-isopropylamino-1,2-propanediol as a degradation product of metoprolol in pharmaceutical dosage forms by HILIC-CAD

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A B S T R A C T

Aryloxypropanolamine is an essential structural motif for a variety of \( \beta \)-adrenergic receptor antagonists such as metoprolol. Molecules with such a structural motif tend to degrade into \( \alpha \), \( \beta \) –hydroxypropanolamine impurities via a radical-initiated oxidation pathway. These impurities are typically polar and nonchromophoric, and are thus often overlooked using traditional reversed phase chromatography and UV detection. In this work, stress testing of metoprolol confirmed the generation of 3-isopropylamino-1,2-propanediol as a degradation product, which is a specified impurity of metoprolol in the European Pharmacopoeia (impurity N). To ensure the safety and quality of metoprolol drug products, hydrophilic interaction chromatography (HILIC) methods using Halo Penta HILIC column (150 mm \( \times \) 4.6 mm, \( 5 \mu \text{m} \)) coupled with charged aerosol detection (CAD) were developed and optimized for the separation and quantitation of metoprolol impurity N in metoprolol drug products including metoprolol tartrate injection, metoprolol tartrate tablets, and metoprolol succinate extended-release tablets. These HILIC-CAD methods were validated per USP validation guidelines with respect to specificity, linearity, accuracy, and precision, and have been successfully applied to determine impurity N in metoprolol drug products.

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1. Introduction

Aryloxypropanolamine is an essential structural motif for a variety of \( \beta \)-adrenergic receptor antagonists including \( \beta_1 \), \( \beta_2 \), \( \beta_3 \), and nonselective agents [1]. Molecules with such a structural motif have been reported to degrade into \( \alpha \), \( \beta \)-hydroxypropanolamine impurities. For instance, aromatic ether cleavage by hydroxyl radical (•OH) was observed for acebutolol, alprenolol, atenolol, metoprolol, and propranolol; \( \alpha \), \( \beta \)-hydroxypropanolamines were detected as degradants under a variety of oxidative conditions such as ozonation [2–5], electrochemical oxidation [6–8], CYP450 metabolism [8], photodegradation [9–14], and aerobic biodegradation [15]. The current European Pharmacopoeia (Ph. Eur.) includes two \( \alpha \), \( \beta \)-hydroxypropanolamines, 1,3-bis(isopropylamino)-2-propanol (impurity M) and 3-isopropylamino-1,2-propanediol (impurity N), as specified impurities for metoprolol tartrate and metoprolol succinate monographs [16,17]. To ensure the safety and quality of the drug substances and drug products, these impurities need to be appropriately controlled. However, development of highly sensitive and selective analytical methods is particularly challenging as \( \alpha \), \( \beta \)-hydroxypropanolamines are typically polar and nonchromophoric; they are poorly retained in a conventional reversed-phase chromatographic system and are invisible for UV detection. Both Ph. Eur. and the United States Pharmacopoeia—National Formulary (USP–NF) use TLC methods for the analysis of this type of impurities [16–19].

Although \( \alpha \), \( \beta \)-hydroxypropanolamines are typically not included as impurities in Ph. Eur. or USP monographs of \( \beta \)-adrenergic receptor antagonists, their presence might be overlooked as the majority of the compendial methods are based on reversed phase HPLC-UV. In previous efforts to modernize the USP–NF metoprolol succinate monograph, a hydrophilic interaction chromatography (HILIC) method coupled with a charged aerosol detector (CAD) for the determination of impurities M and N in metoprolol succinate drug substance was developed and validated [20]. Forced degradation studies of metoprolol tartrate confirmed
the generation of the impurity N as a degradation product under hydrogen peroxide–mediated oxidative conditions (Fig. 1) [20]. According to USP–NF General Chapter <1086>, degradation products that arise during manufacturing process and under recommended storage conditions need to be controlled for drug products [21]; these degradation results and mechanism insights prompted us to extend the HILIC-CAD method to metoprolol drug products including metoprolol tartrate injections, metoprolol tartrate tablets, and metoprolol succinate extended-release tablets. This study exemplifies the importance and utility of HILIC-CAD methods to control the quality of β-adrenergic receptor antagonist drug substances and drug products [22].

2. Material and methods

2.1. Chemicals and reagents

Drug substance metoprolol tartrate or succinate, and sodium chloride were obtained from USP metoprolol tartrate or succinate Reference Standards (Rockville, MD, USA). Commercial samples of metoprolol tartrate tablets, metoprolol tartrate injection, and metoprolol succinate extended-release tablets were purchased from suppliers: three metoprolol tartrate tablets products (100, 50, and 25 mg); three metoprolol tartrate injection products (5 mg/mL, inactive ingredients: sodium chloride and water); three metoprolol succinate extended-release tablets products (25 mg). Impurity N (>95%) was acquired from DL Chiral Chemicals (Princeton, NJ, USA). Formic acid (98%) and ammonium formate (pH 3.2; 100 mM) were from Sigma-Aldrich (St. Louis, MI, USA). Acetonitrile was of LC/MS grade and was from Thermo Fisher Scientific (Waltham, MA, USA). Deionized water was purified in a Milli-Q plus system from Millipore (Billerica, MA, USA).

2.2. Instrument and analytical parameters

HILIC-CAD analyses were performed on a Waters Alliance 2695 Series HPLC system (Milford, MA, USA) equipped with a Thermo Scientific Dionex Corona Ultra RS Charged Aerosol Detector (ESA, Chelmsford, MA, USA). Data acquisition, analysis, and reporting were performed using Waters Empower 3 software. Separations were carried out on a Halo Penta HILIC column (4.6 mm x 150 mm, 5 µm) from Advanced Materials Technology (Wilmington, DE, USA) using a mobile phase system consisting of acetonitrile and ammonium formate buffer (pH 3.2 or 2.8; 100 mM). Nebulizer temperature of CAD was set at 25 °C; nebulizer gas was high-purity nitrogen; internal gas pressure was 35.0 ± 0.1 psi; range was set at 50–100 pA. Analyses were performed at ambient temperature with a flow rate of 0.8 mL/min. Injection volume was 5 µL for injection and 10 µL for tablets. The gradient elution programs are shown in Table 1.

2.3. Solution and sample preparation

Injection: Water was used as diluent. Mobile phase A was composed of ammonium formate (pH 3.2; 100 mM), and mobile phase B was acetonitrile. A resolution solution at a concentration of 0.1 mg/mL for metoprolol tartrate, 0.9 mg/mL for sodium chloride, and 0.01 mg/mL for impurity N was prepared by dissolving each material in the diluent. An impurity stock solution at a concentration of 0.2 mg/mL was prepared by dissolving impurity N in the diluent. The standard solution was prepared at a concentration of 2 µg/mL by diluting the impurity stock solution. The injection product was used directly as the sample solution.

Tablets: The mixture of water and acetonitrile (15:85, v:v) was used as diluent. Mobile phase A was composed of ammonium formate (pH 2.8; 100 mM) and mobile phase B was acetonitrile. A resolution solution at a concentration of 0.1 mg/mL for metoprolol tartrate and 0.01 mg/mL for impurity N was prepared by dissolving each material in the diluent. An impurity stock solution at a concentration of 0.2 mg/mL was prepared by dissolving impurity N in the diluent. The standard solution was prepared at a concentration of 2 µg/mL by diluting the impurity stock solution. The composite of tablets was prepared by grinding and homogenizing 20 tablets into a fine powder using a mortar and pestle. Sample solution was prepared at a concentration of 1.0 mg/mL by dissolving the composite in the diluent.

Method development solution, resolution solution, sample solution for forced degradation, and linearity solutions and spiked solutions for method validation are provided in Supplementary data.

3. Results and discussion

3.1. Forced degradation of metoprolol

The Ph. Eur. metoprolol tartrate and metoprolol succinate monographs include 12 impurities (impurities A–H, J, M, N, and O) using a mobile phase system consisting of acetonitrile and ammonium formate buffer (pH 3.2 or 2.8; 100 mM). Nebulizing temperature of CAD was set at 25 °C; nebulizer gas was high-purity nitrogen; internal gas pressure was 35.0 ± 0.1 psi; range was set at 50–100 pA. Analyses were performed at ambient temperature with a flow rate of 0.8 mL/min. Injection volume was 5 µL for injection and 10 µL for tablets. The gradient elution programs are shown in Table 1.

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while the USP–NF specifies four related compounds (RCs), A, B, C and D (Fig. S1) [16–19]. A solution including 13 metoprolol impurities (12 Ph. Eur. impurities and a different USP impurity RC B) was prepared for method development. Initially a UHPLC-UV method using 0.1% phosphoric acid and acetonitrile as mobile phase was developed which could separate 11 impurities and metoprolol within 5 min (Table S1 and Fig. S2). The method was converted to a similar LC/MS method by replacing the phosphoric acid with trifluoroacetic acid (Table S2). The two nonchromophoric impurities M and N could not be detected by UV, but LC/MS analysis indicated that both co-eluted with the solvent front (Fig. S3).

Forced degradation of metoprolol was conducted by stressing metoprolol tartrate or succinate under thermal, thermal and humidity, hydrolytic (acid and base), photolytic (UVA and Vis), and oxidative conditions [23–25]. All stress samples were monitored by the UHPLC-UV and LC/MS methods; only the oxidative and base stresses produced significant degradation of metoprolol and several impurities, but none of them corresponded to the known impurities (Tables S3 and S4). However, all new peaks were completely separated by both methods; co-elution of the main peak (metoprolol) was excluded based on PDA purity analysis.

In order to monitor the generation of nonchromophoric impurities, the oxidative stress sample was subjected to LC/MS analysis; impurity N was indeed produced under oxidative stress conditions although it co-eluted with solvent front (Fig. S3). The generation of impurity N was further verified using the HILIC-CAD method [20]. Generation of impurity N was observed for H2O2-mediated oxidative stress of both metoprolol tartrate and succinate (Fig. 2). These results, in combination with literature data [2–15], clearly established the necessity of developing HILIC-CAD organic impurities testing procedures for metoprolol drug products.

### 3.2. HILIC-CAD method development

A HILIC-CAD method (Halo Penta HILIC column, 150 mm × 4.6 mm, 5 μm; ammonium formate buffer–acetonitrile, 15:85) was developed for metoprolol succinate drug substance, which separated metoprolol impurities N and M, metoprolol, and succinic acid [20]. For the tablets and injection drug products, the method was slightly modified to accommodate the presence of excipients while maintaining the separation of impurity N from metoprolol and impurity M (Table 1).

**Table 1**

| Parameter | Injection | Tablets |
|-----------|-----------|---------|
| Elution   | Time (min) | A (%) | B (%) | Time (min) | A (%) | B (%) |
| 0.0       | 20        | 80    |       | 0.0       | 15    | 85    |
| 6.0       | 20        | 80    |       | 7.0       | 15    | 85    |
| 6.1       | 80        | 20    |       | 7.1       | 80    | 20    |
| 9.0       | 80        | 20    |       | 9.0       | 80    | 20    |
| 9.1       | 20        | 80    |       | 9.1       | 15    | 85    |
| 15.0      | 20        | 80    |       | 15.0      | 15    | 85    |
| Column    | Halo Penta HILIC (150 mm × 4.6 mm, 5 μm) | Halo Penta HILIC (150 mm × 4.6 mm, 5 μm) |
| Mobile phase | A: ammonium formate buffer, 100 mM, pH 3.2; B: acetonitrile | A: ammonium formate buffer, 100 mM, pH 2.8; B: acetonitrile |
| Diluent   | Water     | Water and acetonitrile (15:85) |
| Column temperature | Ambient | Ambient |
| Flow rate | 0.8 mL/min | 0.8 mL/min |
| Injection volume | 5 μL | 10 μL |
| Detection | CAD; Gas: Nitrogen; Pressure: 35.0 ± 0.1 psi; Range: 100 pA; Filter: 3; Nebulizer temperature: 25 °C | CAD; Gas: Nitrogen; Pressure: 35.0 ± 0.1 psi; Range: 50 pA; Filter: 3; Nebulizer temperature: 25 °C |
impurities M and N and metoprolol. The composition of mobile phase was changed to 80% buffer for 2 min to elute all excipients, and then adjusted back to the initial ratio for 5 min. The 5 min column equilibration time is necessary as CAD methods are generally sensitive towards mobile phase variations.

Injection: As a significant amount of sodium chloride is presented in the formulations, and both sodium and chloride ions could be detected by CAD, the ratio of mobile phase was slightly adjusted (buffer–acetonitrile, 20:80) to maximize the resolution between peaks of impurity N and the chloride ion to 2.0 or higher. Additionally, a 3-min elution step (buffer–acetonitrile, 80:20) was added to the end of the run to minimize the potential interference of sodium chloride in successive injections. Lastly, the injection volume was decreased to 5 μL to avoid the introduction of large amount of sodium chloride to the system.

3.3. Sample preparation

Injection: Since water (solvent of the injection products) was used as the diluent for the method validation, various metal ions from glass vessels were found to slowly dissolve into the solution (within 3–4 h), and could be detected by CAD. Moreover, some ions were poorly resolved from the peak of impurity N, and adversely affected the peak integration. Therefore, polypropylene volumetric flasks and autosampler vials were used for solution preparation to eliminate the interference of metal ions from glass vessels. In addition, the use of LS/MS grade acetonitrile is highly recommended. The simple formulation of injection products allowed the preparation of a stock sample solution at higher concentration (2.5 mg/mL) by mixing metoprolol tartrate and sodium chloride at the same ratio as samples, and dissolved in water.

3.4. Method validation

The modified HILIC-CAD methods demonstrated the complete separation of impurity N from all other components, including excipients (Fig. 3). The separation of impurity N from impurity M was maintained as minimal variations of mobile phase composition.

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Fig. 3. HILIC-CAD separation of impurity N in metoprolol drug products: (A) Metoprolol tartrate injection, (B) Metoprolol tartrate tablets, and (C) Metoprolol succinate extended-release tablets. From bottom to top in each overlaid chromatogram: standard solution of impurity N, sample solution of the drug product, and sample solution spiked with impurity N at 0.2% level.
were involved. Robustness studies of the original method revealed that such variations will not compromise the resolution of impurity N from impurity M [20]. Impurity N was also separated from that such variations will not compromise the resolution of impurity N [20]. Impurity N was also separated from impurity M [20] and adjacent peaks, and reproducibility and specification for multiple injections) were met for the primary validation study and for intermediate precision (Tables S5–7).

Although aerosol-based detectors are considered to be non-linear over a wide concentration range [22], linear responses can be obtained for a variety of analytes within a narrow concentration range and at low concentrations. Linearity in the concentration range of 1.0–3.0 µg/mL (50%–150% of the concentration of the impurity at the proposed limit) was demonstrated for method validation of impurity N. Linearity in a wider concentration range (1–10.0 µg/mL) was also verified for metoprolol tartrate tablets. Correlation between area and the concentration for both ranges exceeded 0.99 for impurity N. It should be mentioned that the linearity range is sufficient for the compendial method validation, as the limit for impurity N was established based on ICH guidelines at 0.2%, the linearity ranges covered 0.1%–0.3% of impurity N, which is sufficient for the drug product impurity control.

Accuracy of the method was established by evaluating recoveries obtained with 15 spiked solutions at the 0%, 50%, 100%, and 150% impurity levels (Table 2). Precision was estimated by evaluating six spiked solutions at the 100% impurity level. Recovery was calculated by comparing the theoretical concentration calculated from the calibration curve and the nominal concentration. The results of accuracy and precision analyses are summarized in Table 2. The accuracy of the method was established by the fact that recoveries across all data points were between 96.8% and 103.3%. The precision of the method was confirmed in that relative standard deviation (RSD) values of impurity N at the 50%, 100%, and 150% levels were less than 3%. These data indicated that the HILIC-CAD methods are accurate and repeatable for quantitation of impurity N in the drug products tested.

Intermediate precision was determined by a second scientist on a different day using the same type of column but a different lot number of the same manufacturer. The accuracy and precision results from the analysis of intermediate precision also met the criteria (Table 2). The average combined recoveries of 12 samples at 100% level analyzed by the first and second chemists were 99.3–100.2%, and the combined RSDs were less than 3%.

Chromatograms and detailed validation results for the three drug products were provided in Supplementary data.

3.5. Application

The developed HILIC-CAD methods were applied to determine organic impurities in the metoprolol drug product samples from various manufacturers. The results indicated that impurity N was either below the limit value or not detected in all drug products tested. Toxicity assessment of impurity N has never been reported; toxicity of impurity N at concentration below ICH limit is less likely.

4. Conclusions

HILIC-CAD methods were developed for the determination of the nonchromophoric impurity N in metoprolol drug products. The separation of impurity N from metoprolol, other impurities, and excipients was achieved on a Halo Penta HILIC column with a mobile phase comprising acetonitrile and ammonium formate buffer (pH 3.2 or 2.8; 100 mM). The HILIC-CAD method was subsequently validated for specificity, linearity, accuracy, and precision. In addition to the current HPLC-UV organic impurities procedure, the method may also be used as an additional organic impurities procedure for metoprolol drug products.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2019.08.001.
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