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The influence of inorganic salts with chaotropic properties on the chromatographic behavior of ropinirole and its two impurities

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ABSTRACT

Chaotropic agents recently gained popularity as interesting and useful mobile phase additives in liquid chromatography due to their effect on analytes retention, peak symmetry and separation efficiency. They mimic the role of classical ion-pairing agents, but with less drawbacks, so their use becomes attractive in the field of pharmaceutical analysis. In this paper, the influence of sodium trifluoroacetate and sodium perchlorate on the chromatographic behavior of ropinirole and its impurities is examined. By the extended thermodynamic approach, it was shown that the separation in the given system was predominantly governed by electrostatic interactions between the protonated analytes and the charged surface of the stationary phase, but the ion-pair complex formation in the eluent also proved to be significant. Further, the employment of face-centered central composite design enabled the understanding of the effect of chaotropic agent concentration and its interactions with other factors (acetonitrile content and pH of the water phase) that influence the given chromatographic system. Finally, the same data was used for multi-objective optimization based on the grid point search method. After the method validation, the adequacy of the suggested approach in development of methods for routine pharmaceutical analysis was proven.

1. Introduction

The interest for simple inorganic chaotropic agents was renewed in recent years due to their ability to increase the retention of the oppositely charged analytes, also improving the peak symmetry and separation efficiency when used as mobile phase additives in liquid chromatography [1–8]. They mimic the role of classical ion-pairing agents, but with fewer drawbacks. Unlike classical ion-pairing agents that stick strongly to the stationary phase, chaotropic additives can be easily dissolved in mobile phase, so their impact on the initial column properties is reversible thus enabling longer column life.

These attractive properties of chaotropic agents can be of a great value in the pharmaceutical method of development strategies. However, the complexity of the chaotropic system requires special attention and detailed understanding of chaotropic agents' effects on chromatographic systems behavior, so in order to rationalize this approach it is necessary to understand the mechanism that underlies it. Therefore, the aim of this paper was to present detailed strategy for the examination of different chaotropic agents' influence and the thorough approach in selection of the proper chromatographic conditions on the example of mixture consisted of ropinirole (4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one) and its structurally related impurities A (4-[2-(propylamino)ethyl]-1,3-dihydro-2H-indol-2-one) and C (4-[2-(dipropylamino)ethyl]-1H-indol-2,3-dione) (Fig. 1). Ropinirole is a non-ergoline dopamine agonist specific for D2 and D3 dopamine receptors approved in the therapy of Parkinson's disease and restless leg syndrome. Several reversed-phase high-performance liquid chromatography (RP-HPLC) methods were developed for the analysis of ropinirole in bulk and dosage forms [9–11] and for the stability profiling [12,13]. The simultaneous separation and quantification of ropinirole and some impurities were achieved by capillary liquid chromatography [14] and by RP-HPLC using sodium alkylsulphonates as ion-pair reagents [15,16].

In this study, the examined agents with chaotropic properties were sodium trifluoroacetate (NaTFA) and sodium perchlorate (NaClO4). The description of the separation phenomena was achieved through the retention modeling from the theoretical and empirical aspects. The extended thermodynamic approach suggested by Cecchi et al. [17,18] enabled a comprehensive consideration of both the ion-pair complex formation and the double layer development. Further, the method development of the examined mixture was governed by the design of experiments methodology. This approach allowed the understanding of additional chromatographically relevant parameters as well as their interactions with chaotropic agents. Finally, the grid point search

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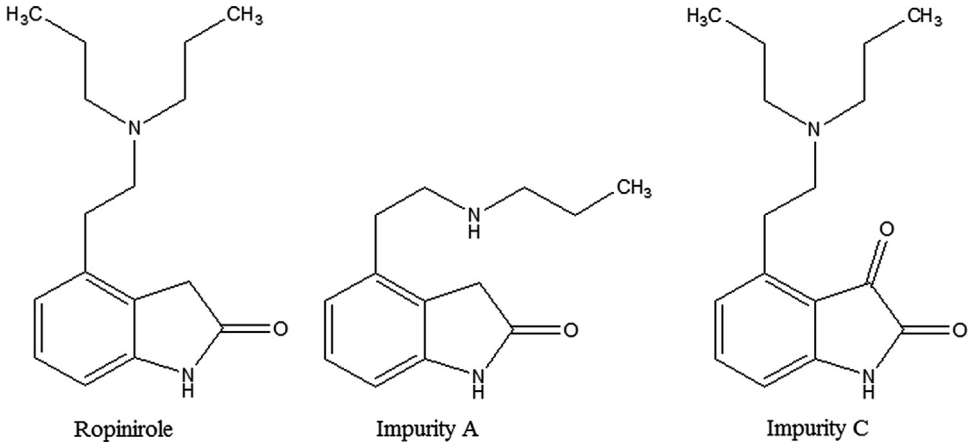

Fig. 1. Chemical structures of the analyzed substances.

method enabled the identification of the optimal chromatographic conditions and the method was fully validated.

2. Material and methods

2.1. Chemicals

All chemicals used were of the analytical grade. Acetonitrile (Fluka, Sigma-Aldrich, Steinheim, Germany), sodium perchlorate monohydrate (Fluka, Sigma-Aldrich, France), sodium trifluoroacetate (Aldrich, Sigma-Aldrich, USA), *ortho*-phosphoric acid (J.T. Baker, Deventer, Holland) and water (HPLC grade) filtered through Simplicity 185 (Millipore, Billerica, MA) were used for the preparation of the mobile phases. Standards of ropinirole and its impurities A and C were obtained from LGC GmbH, Luckenwalde, Germany. The dosage form used for method validation was Requip™ tablets (GlaxoSmithKline, UK).

2.2. Solutions

Stock solutions were prepared by dissolving the respective amounts of standard substances in the mixture acetonitrile–water (50:50, v/v) to obtain the concentrations of 500 μg/mL for ropinirole and 100 μg/mL for its impurities A and C.

Stock solutions were further diluted to obtain a mixture of 50 μg/mL for ropinirole and 1 μg/mL for the impurities. This mixture was used to obtain the chromatographic data for thermodynamic retention modeling and for the method optimization.

2.3. Solutions for the selectivity estimation

A mixture of the excipients–blank sample was prepared in the concentration ratio corresponding to the content in tablets. It was treated in the same manner as the tablet mass used for precision estimation. A standard solution mixture containing 200 μg/mL of ropinirole and 1 μg/mL of each impurity was used to prove the method selectivity.

2.4. Solutions for the linearity estimation

For the calibration curve, six solutions containing ropinirole (100–350 μg/mL) and seven solutions for the impurities A and C (0.1–1.2 μg/mL) were prepared from the corresponding standard solutions.

2.5. Solutions for the accuracy estimation

The laboratory mixtures containing blank sample and ropinirole, and blank sample and the impurities were prepared in the mixture of acetonitrile–water (50:50, v/v) and sonicated in the ultrasonic bath for 30 min. For the accuracy analysis of ropinirole, three series of three solutions in 80%, 100% and 120% concentration levels were prepared. For the analysis of the impurities accuracy, three series of three solutions in the limit of quantification (LOQ), 100% and 120% concentration levels were prepared.

2.6. Solutions for the precision estimation

For the precision estimation, a quantity of pulverized tablet mass corresponding to 25 mg of ropinirole was placed into a 50 mL volumetric flask and extracted with the mixture acetonitrile–water (50:50, v/v) using the ultrasonic bath for 30 min. The volumetric flask was filled to the mark with the same solvent, and the solution was filtered. From that stock solution, six solutions containing 200 μg/mL of ropinirole were prepared. Since the present impurities were below the limit of quantification, the precision was estimated from the replicates of laboratory mixture prepared for the accuracy testing.

2.7. Equipment

The experiments were performed on the chromatographic system Finnigan Surveyor Thermo Scientific consisted of HPLC Pump, Autosampler Plus and UV/VIS Plus Detector. ChromQuest was used for data collection and analysis. The volume of the injector sample loop was 25 μL, while the partial loop injection volume was 5 μL. Chromatographic separations were performed on XBridge® C18, 150 mm × 3 mm, 3.5 μm particle size column (Waters, Ireland). Column surface area was 99.1 m^2/column. Full details of the column properties are given in [19].

2.8. Chromatographic conditions

To collect the data necessary to build the thermodynamic model, the experiments were performed in isocratic mode. The mobile phase consisted of acetonitrile and aqueous phase (containing different amounts of NaTFA or NaClO4 and pH adjusted to 2.5 with *ortho*-phosphoric acid) 15:85 (v/v). Column temperature was set at 30 °C, while the flow rate was 0.7 mL/min. Detection was carried out at 250 nm.

For the determination of the adsorption isotherms of chaotropic agents, frontal chromatograms were performed using a gradient