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Simultaneous determination of the counter ion and possible impurity from the synthetic route in the pharmaceutical substance prasugrel hydrochloride

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ABSTRACT

A fast and selective capillary electrophoresis method was developed and validated for the simultaneous determination of the hydrochloride and acetic acid content in prasugrel hydrochloride. Because of the poor chromophore, the indirect detection was chosen. Among different compositions studied as the background electrolyte, the pyromellitic acid with diethylamine (DEA) and myristyltrimethylammonium bromide (TTAB) was chosen. During the validation the specificity, linearity, accuracy, precision, range, and stability of the sample solution were confirmed. The results indicate that the method is suitable for the determination of the counter ion and impurity from the synthetic route of the pharmaceutical drug substance in the same assay

1. Introduction

The determination of small organic and inorganic ions is an important part of a pharmaceutical analysis. Many drug molecules are charged and are manufactured with the counter ion. Hence, it is important to analytically characterize the drug stoichiometry to ensure that the potency of the batch of the drug substance is known. On the other hand, small organic and inorganic ions could be impurities coming from the synthetic route. The task of impurity determination in a drug is therefore of principle importance.

Prasugrel is the most recent member of the thienopyridine class of antiplatelet agents [1]. Similarly to other thienopyridines, it is commonly used in the therapy of choice for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with stent implantation [2,3]. The registered medication brands with prasugrel contain the active substance (API) in the form of hydrochloride salt. Throughout the past two decades several syntheses of prasugrel have been described [4–8]. In general, the original route was based on the formation of 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydro- thieno[3,2-c]pyridin-2(4H)-one (**3**) from the 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)-ethanone (**1**) and 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4H)-one (**2**), followed by the *O*-acetylation with acetic anhydride in N,N dimethylformamide/sodium hydride system. In our synthetic procedure the last steps comprise the *O*-acetylation of 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4H)-one (**3**) to the compound (**4**), in basic reaction conditions and in the presence of acetic anhydride (Fig. 1), then the formation of the prasugrel salt (**5**). During the coupling reaction workup the acetic anhydride may convert to acetic acid or its salts followed by the acetic acid formation as an impurity in the final procedure for obtaining prasugrel hydrochloride.

The determination of small organic and inorganic ions in a pharmaceutical analysis involves mainly the ion chromatography (IC), flame atomic absorption spectrometry and flask-based methods e.g. titration [10]. For volatile solvents determination in pharmaceuticals the gas chromatography (GC) method is recommended and currently used [11]. These methods are reliable and efficient but time, reagent and cost-consuming. Compared to other analytical methods for small organic and inorganic ions determination the capillary electrophoresis technique (CE) has the advantage of using smaller sample amounts with minimal sample preparation, in addition to being fast and efficient. The suitability of analytical methods for small ions determination is restricted by their limited absorbance properties. The CE method has the advantage of offering the possibility of indirect UV detection, in which a chromophore

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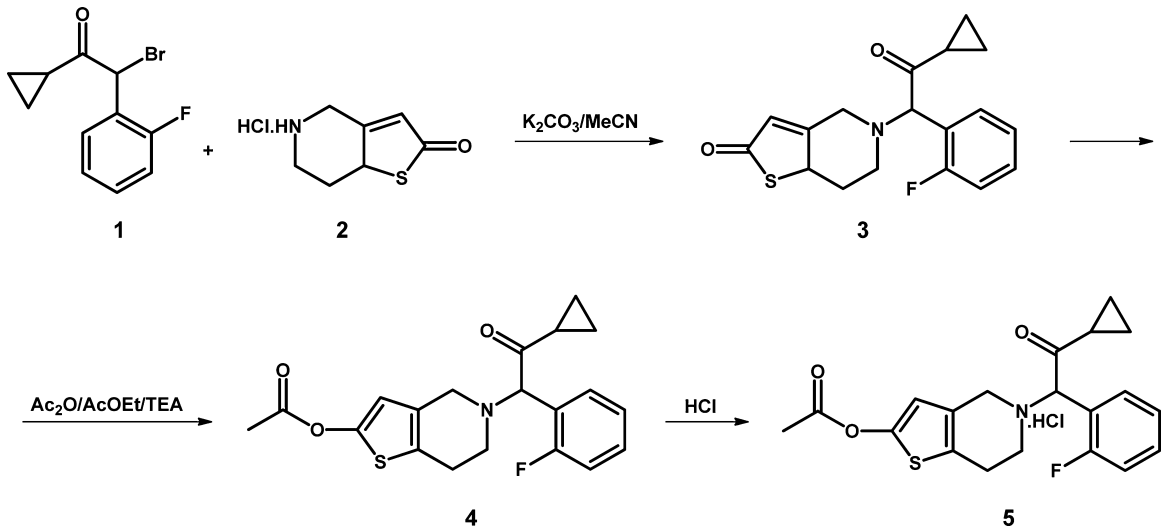

Fig. 1. Prasugrel hydrochloride synthesis [9].

added to the background electrolyte (BGE) is usually applied, which offers low but in most cases sufficient sensitivity. This mode of detection is possible using commercial, most common CE equipment and the UV detectors can be used without any modifications. During the past decade many original and review papers as well as monographs have mentioned the counter ions or impurities determination in drugs [12–20]. The parallel analysis of the counter ion, impurity and pharmaceutical substance is often achieved using the dual-opposite end injection and contactless conductivity detection [13,14,21]. But to the best of our knowledge no validated CE method with indirect detection for the simultaneous counter ion and impurity ion determination in a pharmaceutical substance has been described. This work presents the application and validation of the CE method with indirect UV detection for the simultaneous determination of the counter ion and possible impurity from the synthetic route in prasugrel hydrochloride. The use of the described method provides a beneficial alternative and replaces two expensive and time-consuming, routine methods: the titrimetry and GC, which is an advantage from the point of view of the pharmaceutical analysis. The results obtained during the validation indicate that the method is sufficient to apply for the quality control of the manufacturing batches of prasugrel hydrochloride.

2. Material and methods

2.1. Materials

Prasugrel hydrochloride (batches no.: PU-5/238/043/5/VII and PU-5/140313) and prasugrel base (batch no. PU-4/140313) were manufactured in Pharmaceutical Research Institute, Warsaw, Poland. 1,2,4,5-benzenetetracarboxylic acid (PMA) pure p.a., myristyltrimethylammonium bromide (TTAB) pure p.a., cetyltrimethylammonium bromide (CTAB) pure p.a., tetrabutylammonium hydroxide solution pure, salicylic acid pure p.a., 2,6-naphtalenedicarboxylic acid (NDC) pure p.a. and sodium chloride pure p.a. were purchased from Sigma–Aldrich, Steinheim, Germany. Diethylamine (DEA) pure p.a., chromium oxide pure p.a., *p*-toluenesulfonic acid pure p.a., ammonium acetate pure p.a., ortho-phosphoric acid pure p.a., Methanol (HPLC grade) and acetonitrile (HPLC grade) were purchased from POCh, Gliwice, Poland. 1.0 N sodium hydroxide solution, 0.1 N sodium hydroxide solution and 0.1 N phosphoric acid solution were purchased from Agilent Technologies, Waldbroon, Germany.

2.2. Instrumentation

Electrophoretic measurements were carried out with ^{3D} Capillary Electrophoresis Instruments G1600A, Agilent Technologies, using uncoated fused-silica capillaries with the total length of 40 cm, length to the detector 32 cm, 50 μm i.d. purchased from Agilent Technologies. The data collection and analysis were carried out using the Agilent Technologies ^{3D} CE ChemStation software. The UV indirect detection was performed using the diode array detector (DAD) with 214 nm wavelength. The samples were injected hydrodynamically by applying 50 mbar pressure during 6 second and the separation voltage was chosen as 25 kV, with negative polarity. The temperature of the capillary cassette was set as 25 °C.

The obtained peak areas were converted to values normalized by the migration time.

2.3. Capillary, background electrolytes and sample preparation

2.3.1. Capillary conditioning

Before use, a new capillary was conditioned with 1 N NaOH for 30 min, then rinsed with deionized water and the background electrolyte for 15 min each. Before daily operation the capillary was rinsed with 0.1 N NaOH, deionized water and the background electrolyte for 15 min each. Prior to each injection the capillary was rinsed using the following procedure: 0.1 N H_3PO_4, deionized water, 0.1 N NaOH and deionized water for 1 min each, then with the background electrolyte for 3 min.

2.3.2. Background electrolyte (BGE) preparation

All BGEs were prepared using deionized water, ultrasonicated for 5 min and filtered through the 0.2 μm Syringe-Driven Filter Unit Millex®-GN, Millipore, Carrigtwohill, Ireland.

Water used in this study was purified and deionized using the Polwater System D-300, Cracow, Poland. Phosphoric acid was used for the pH adjustment.

2.3.3. Solution preparation

The stock standard solutions of chloride (13 mg/mL) and acetate (0.74 mg/mL) were prepared by dissolving an appropriate amount of sodium chloride and ammonium acetate, respectively, in the mixture of deionized water and methanol (1:1, v/v).

These stock solutions were then diluted to the required concentrations with the mixture of deionized water and methanol (1:1, v/v).