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Original Article

A validated capillary electrophoretic method for the determination of indacaterol and its application to a pharmaceutical preparation

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ABSTRACT

Indacaterol is a new inhaled ultra-long acting β_2-agonist. It has been recently approved in the European Union for the treatment of chronic obstructive pulmonary disease. This paper reports, for the first time, a method for the determination and validation of Indacaterol (IND) using an internal standard in capsules. Capillary electrophoretic separation was performed on an uncoated fused-silica capillary (50 cm effective length, 75 μm i.d.) and background electrolyte composed of 20 mmol L^{-1} of sodium tetraborate buffer, 15% (v/v) methanol (pH = 10.0) with the application of 20 kV of potential; 10 s at 5×10^3 N m^{-2} (50 mbar) of injection time; and wavelength of 200 nm and 25 °C of temperature. The linearity was evaluated in the range of 4.90×10^{-6} mol L^{-1} (2.50 μg mL^{-1}) and 3.94×10^{-5} mol L^{-1} (20.00 μg mL^{-1}), with R = 0.9993 for inter-day. LOD and LOQ values were 2.18×10^{-8} mol L^{-1} (0.011 μg mL^{-1}) and 7.25×10^{-8} mol L^{-1} (0.037 μg mL^{-1}) for inter-day, respectively. The precision values were 0.50–1.06% for intra-day and 2.12% for inter-day as RSD%. The accuracy was tested by the standard addition method with the recovery values being between 98.79 and 99.09 as percentages with RSD% interval of 0.01–0.80. The developed method was validated according to ICH guidelines. Indacaterol was successfully determined in Arcapta® capsule dosage form by the validated CE method with a relative error of 0.28%. The result was within the requirements of the USP 34-NF29. Therefore, the validated method may be used for the determination of Indacaterol in its capsules in quality control laboratories.

1. Introduction

Indacaterol (IND) 5-{(1R)-2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1 hydroxyethyl}-8-hydroxy-2(1*H*)-quinolinone maleate (Fig. 1) is a new, once daily orally inhaled, pre-metered single-unit dose capsule-based dry powder ultra-long acting β_2-agonist which has been recently approved in the European Union for keeping the airways open in adults with chronic obstructive pulmonary disease (COPD) [1]. It has also recently been approved

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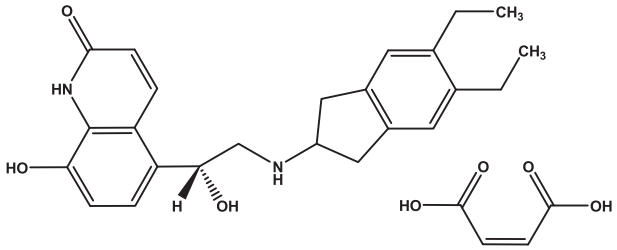

Fig. 1 – The chemical structure of IND.

for COPD by the U. S. Food and Drug Administration (FDA) [2]. COPD is a long-term disease where the airways and air sacs inside the lungs become damaged or blocked, leading to difficulty breathing air in and out of the lungs [3]. Certain drug combinations, such as indacaterol/glycopyrronium dose combination, have also been used for the symptomatic control of COPD in adults. It should be emphasized that local prescribing information should be soughted for details of contraindications, special warnings and precautions relating to the use of these kinds of combinations [4]. As a consequence, analytical methods are required for both supporting indacaterol's pharmacological properties, therapeutical efficacy and tolerability studies [4–6] and for an understanding of these combinations. Currently, a number of publications have been reported for the determination of IND in pharmaceutics [7,8] and other samples [9–13]. The methods employed are spectrophotometry and fluorometry [8,14,15] and HPLC [16] in pharmaceutical preparations, HPLC-MS in human plasma, serum or urine for the determination of IND [9,10,17].

Capillary electrophoresis (CE) is a relatively new and extremely powerful technique. It offers numerous advantages over conventional chromatographic methods because of its unique separation mechanism, speed, higher efficiency, versatility, environmental friendliness, resources utilization, small sample amount, not requiring further purification, and permitting several kinds of buffers and additives usage as the electrolyte [18,19]. Moreover, the sensitivity of CE is generally better than that of HPLC in UV absorbance detection due to the short path length of CE [18,20]. CE has many applications in biochemistry, pharmaceutical science [21], bioscience [22], ion analysis [23], food analysis [24–26] and environmental science [23] fields. To the best of our knowledge, no other publication has addressed the determination of IND by capillary electrophoresis (CE) or capillary zone electrophoresis (CZE). Here we describe the new environmental-friendly, fully validated CE method for the determination of IND in pharmaceutical formulation.

2. Materials and methods

2.1. Chemicals, reagents and samples

HPLC grade methyl paraben (Internal standard, IS), methanol (MeOH), and acetonitrile (ACN) were purchased from Sigma–Aldrich (St. Louis, MO, USA). ACS grade sodium tetraborate and sodium phosphate were purchased from Merck GmbH (Darmstadt, G). Indacaterol maleate (IND) was purchased from Santa Cruz (Santa Cruz Biotechnology, Inc., 10410 Finnell St., Dallas, USA). Ultrapure water with a resistivity of 18.2 μS cm^{-1} (Millipore, Molsheim, France) was used throughout this work. Arcapta® was supplied from Novartis (Novartis Pharma Stein AG, Switzerland).

2.2. Apparatus

All CE separations were conducted on a Capillary Electrophoresis 1600 system with diode array UV detector (Agilent Technologies, G1600 A, Oregon, USA). Electrophoresis was performed in fused silica capillaries of 75 μm i.d. and of effective length of 50 cm and total 57 cm long (Agilent). Gas bubbles from all solutions and samples were removed by ultrasonic bath Sonorex (Bandelin, Berlin, G) and they were then centrifuged in a 4000 rpm speed centrifuge (Sigma, 1-6P Laboratory Centrifuge). The solutions' pH was measured using a model *pH/Ion meter- 720A* with an Orion 71-03 glass electrode (ThermoOrion Beverly, MA 01915-6199, USA). All of the buffers and sample solutions were filtered through a regenerated cellulose (RC) membrane filter 0.45 μm prior to analysis (La-Pha-Pack, Rockwood, TN, USA).

2.3. Solution and sample preparation

A stock solution (4.92×10^{-4} mol L^{-1}) was prepared by dissolving 25 mg of IND in 100 mL MeOH. Serial dilutions were performed with the 10% (v/v) MeOH/water mixture to obtain the appropriate concentration range. The standard solutions were stable for at least two weeks if kept in a refrigerator at +4 °C.

15.2 mg methyl paraben (IS) was dissolved in 30 mL of MeOH and was then diluted with ultrapure water up to 100 mL.

A stock sodium tetraborate buffer solution (100 mmol L^{-1}) was prepared, and then relevant running buffer solutions were obtained from this solution. The pH of the solution was adjusted to a desired value with 0.1 mol L^{-1} HCl or 0.1 mol L^{-1} NaOH. This was prepared daily by mixing appropriate volumes of stock buffer solutions, water and MeOH in order to adjust the pH to the desired value.

Each inhalation powder hard capsule (Arcapta®) contains 194 μg of indacaterol maleate, equivalent to 150 μg of indacaterol and certain inactive ingredients, such as lactose monohydrate and gelatine. Ten capsules were accurately weighed individually taking care to preserve the identity of each capsule. The contents of each capsule were removed. The emptied shells were then individually accurately weighed, and the net weight of contents for each capsule was calculated by subtracting the weight of shell from each respective gross weight. The drug substance content of each capsule was calculated from the net weight of the individual capsule content. The drug substance content of each capsule (25.3 mg of Arcapta®) was transferred into a small flask and extracted with 3 mL of MeOH. The mixture was centrifuged at 4000 rpm for 5 min and then filtered through a 0.45 μm membrane filter (RC). A 0.1 mL aliquid of the sample solution was diluted to 1 mL with water. Then 30 μL of IS at 1.05×10^{-3} mol L^{-1} was added. Finally, it was injected through the CE capillary.

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