Review Article

Analytical Methods for Estimation of Indacaterol Maleate in Pharmaceutical Dosage Form and Biological Fluids – A Review

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ABSTRACT

Indacaterol Maleate is a novel class of β_2 adrenoreceptor -agonist used to treat chronic obstructive pulmonary disease. Various analytical methods used for the estimation of Indacaterol Maleate has been reviewed in this paper. These include Ultraviolet Spectrometric, High performance liquid chromatography method for qualitative and quantitative estimation of Indacaterol maleate in pharmaceutical formulations and biological fluids.

Keywords: Indacaterol Maleate, Analytical methods, Formulation, Biological fluids.

INTRODUCTION

Indacaterol Maleate (IND) is chemically known as 2-[(5, 6-Diethyl-2, 3-dihydro-1H-inden-2-yl) amino]-1-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one**. (Fig.1)** IND stimulate adrenergic β_2 receptors in the smooth muscle of the airways. IND prevents airway spasms caused by chronic obstructive pulmonary disease (COPD). This drug is indicated for the treatment of COPD. This causes relaxation of the muscle, thereby increasing the diameter of the airways, which becomes constricted in asthma and COPD.

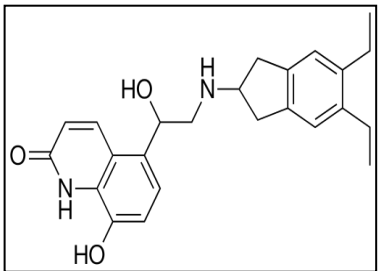

Fig. 1: Chemical Structure Indacaterol Maleate

IND is a new long acting β2- agonist bronchodilators and its long action due to its high affinity to the lipid raft domains in the airway membrane so it slowly dissociates from the receptors at dose 150-300 mg/day. Indacaterol maleate rapidly absorbed following oral administration and widely distributed throughout the body with apparent volume of distribution 10±4L/kg. It shows 94.1-95.3% and 95.1-96.2% plasma protein binding [6]. It is extensively metabolised Indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the pre dominant is enzyme responsible for hydroxylation of Indacaterol metabolites which are excreted in urine (2-5%) and faeces (23-54%) . At least 20 metabolites have been detected but only 2-[(5,6-Diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one is active metabolite. Elimination occurs mainly through hepatic metabolism. Less than 2% of orally administered dose is excreted unchanged in urine and faeces. Only small quantities are excreted in the breast milk. The tolerability of INDA is 1 year. The main side effects of IND even with overdosing are nasopharyngitis cough, upper respiratory tract infection and headache tachycardia, tremor, palpitations, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

High degree of safety of Indacaterol maleate leads to better compliance and higher efficacy of therapy in patients. Recent studies suggest that INDA can be beneficial for the treatment of COPD.

ANALYTICAL METHODS FOR INDACATEROL MALEATE

Many different analytical methods have been reported for the estimation of Indacaterol Maleate in bulk and dosage form as well as in biological fluids.

FOR ESTIMATION IN BULK DRUG AND PHARMACEUTICAL FORMULATION

Spectrometric methods

Y.A. Salem et al.[7] developed Spectroscopic method for estimation of Indacaterol maleate in capsules. Three simple and sensitive spectrophotometric methods (A, B and C) have been developed for the quantitative estimation of Indacaterol maleate (IND) in bulk drug and capsules.

Method A was based on the measurement of the difference absorption spectra of IND in 0.1 N HCl and 0.1 N NaOH media. The difference spectrum exhibits maxima and minima at 274.6 and 257.8 nm, respectively. The method was found to be linear in the concentration range of 1 to 16 µg/ ml with percent recovery of 99.37% - 100.19%. The LOD and LOQ were found 0.07 µg /ml and 0.212 µg /ml respectively.

Method B was based on the oxidative coupling reaction with an acidic solution of the chromogenic agent 3-methylbenzothiazoline-2-one hydrazone (MBTH) and the drug upon treatment with ceric ammonium sulphate (CAS) produces an orange colour peaking at 545 nm. The method was found to be linear in the concentration range of 2 to 20 µg/ ml with percent recovery of 99.51% - 99.90%. The LOD and LOQ were found 0.213 µg /ml and 0.651 µg /ml respectively.

Method C was based on the reaction with 4-aminoantipyrine (4-AAP) in presence of alkaline oxidizing agent; potassium hexacyano ferrate and diluted ammonia (K3 [Fe (CN) 6] / NH3) and measuring the produced red colour at 510 nm. Beer's law is obeyed in the concentration range of 3.0 – 30.0 µg /ml with percent recovery of 99.60 - 100.54 %. The LOD and LOQ were found 0.125 µg /ml and 0.38 µg /ml respectively.

Method A was found to be the most sensitive method providing the highest molar absorptivity and specific absorbance values. For application in quality control laboratories, method A is considered superior to other methods owing to its rapidness, minimum steps, simplicity and sensitivity providing high rates of sample throughput. Both methods A and C employ simple diluting solvents (0.1 N HCl, NaOH and distilled water, respectively) providing cost effectiveness. However, distilled water is more eco-friendly. The proposed methods are applicable and valid for the assay of Indacaterol maleate. They have the advantages of being less time-consuming and don't require elaborate treatments and expensive solvents required with the chromatographic methods.

The increasing order of sensitivity of the propose methods are A > B > C, so the proposed spectrophotometric methods can be used in the determination of Indacaterol in bulk drug and its capsules in quality control laboratories without the interference from common excipients.

The proposed method was found to be useful for routine analysis of pharmaceutical formulation.

Maha F, et al.[8], developed Spectroscopic method for estimation of Indacaterol maleate and glycopyrronium in a newly approved pharmaceutical formulation using different signal processing techniques of ratio spectra.

Three spectrophotometric methods have been developed and validated for determination of Indacaterol (IND) and glycopyrronium (GLY) in their binary mixtures and novel pharmaceutical dosage form. The proposed methods are considered to be the first methods to determine the investigated drugs simultaneously. The developed methods are based on different signal processing techniques of ratio spectra namely; Numerical Differentiation (ND), Savitsky–Golay (SG) and Fourier Transform (FT). The developed methods follow Beer's law over concentration range 1–30 and 10–35 (µg/mL) for IND and GLY, respectively. The percentage recoveries range was found 99.00%–100.49%. The developed methods were proved to be specific, sensitive, precise and accurate for estimation of the investigated drugs in their pharmaceutical dosage form.

Chromatographic methods

The high performance Liquid chromatography (HPLC) method has been reported for the analysis of INDA in pharmaceutical formulation as well as in bulk.

Y. A. Salem et al.[9] Developed high performance Liquid chromatography for determination of Indacaterol Maleate in Pharmaceutical Preparations adopting Ultraviolet and Fluorescence Detection. The chromatographic separation was performed on C18 column as a stationary phase, and the mobile phase consisted of acetonitrile: 5mM acid hydrogen orthophosphate containing 0.3 % triethylamine (TEA) in ratio of (40: 60% v/v) adopting both Ultraviolet and fluorescent detection adjusted to pH 3.0 using 0.02 M orthophosphoric acid (OPA) and was passed at flow rate 1.0 mL /min. The UV detection was adjusted at 259 nm where dexamethasone was used as internal standard or fluorescence detection was at 421 nm after excitation at 258

nm where Cyproheptadine was used as internal standard. The retention time for INDA was 2.906 min. The proposed method was simple, economical, accurate and rapid for estimation of IND. The method was found to be linear in the concentration range of 2 to 20 µg/ ml with LOD of 0.116 µg/ ml and LOQ of 0.352 µg/ ml adopting UV detection. While the linearity range was 0.05 – 5.0 µg/ ml with LOD of 8.6×10^{-3} µg/ ml and LOQ of 26.1×10^{-3} µg/ ml adopting fluorescent detection. The proposed method was rapid reproducible precise and accurate. This method was applied successfully to determine IND in pure form and in its capsule dosage form. The developed method adopting fluorescent detector is 50 times more sensitive than Ultraviolet method.

FOR ESTIMATION IN BIOLOGICAL FLUIDS

There are few methods available for estimation of Indacaterol Maleate in biological matrices like plasma and urine. Case reports on estimation of Indacaterol Maleate had also been reported.

Human Plasma

Wesam G. Et al.[10] developed and validated Liquid Chromatography-Tandem Mass Spectrometry Coupled with Liquid-Liquid Extraction for Indacaterol Quantitation in Human Plasma. The HPLC analytical column was a Reprosil 100 C18 (150 × 4.6 mm, 5µm). Ethyl acetate was used in liquid – liquid extraction (LLE) method to extract IND from plasma sample. The Indacaterol dry extract was then reconstituted with 200mm of the mobile phase which was simply an acidified mixture of water-methanol (30:70, v/v) then pumped at flow rate of 1 ml/min and detected at 421 nm. Formoterol was used as the internal standard. IND and IS were detected at mass to charge ratio of 393.3 and 345.2 respectively. The retention time (t_R) of IND and IS were 2.5 and 1.5 min. The calibration curve was found to be linear over 0.075-100ng/mL. Validation has confirmed a specific, accurate and precise HPLC-MS/MS coupled with a simple and fast LLE for Indacaterol in human plasma. The proposed method was found to be suitable for the clinical monitoring of patients treated with IND.

Human Urine

Wesam G. et al.[11] developed LC-MS for estimation of Indacaterol in Human Urine. A liquid–liquid extraction method has been developed to extract Indacaterol from human urine samples using ethyl acetate. Indacaterol dry extract was reconstituted with 200 µL of the mobile phase (acidified water: methanol (30:70, v/v) of which 5 µL was needed for the HPLC-MS/MS analysis. Indacaterol was eluted on a reversed C18 stationary phase with an isocratic mobile phase at a flow of 1 mL/min. Formoterol was the internal standard (IS). The MS/MS detection was employed with turbo-ion spray ionization in the positive ion mode. Indacaterol was detected at a mass to charge ratio (m/z) of 393.3 and its MS/MS daughter at 173.2. The retention times of IND and IS were 1.60 and 1.20 min. Validated calibration curves were linear over a range of 0.075–100 ng/mL with correlation coefficients r^2= 0.990. The percentage recovery of IND was 92.2%. The proposed had been validated for quantification of Indacaterol in human urine.

CONCLUSION

Several analytical methods have been reported for the estimation of Indacaterol Maleate in pharmaceutical formulations and biological matrices. It can be concluded that UV spectrophotometry and HPLC are the most simple and accurate methods for IND estimation in pharmaceutical formulations while HPLC-UV and LC/MS/MS can be widely used for estimation of IND in biological fluids like plasma and urine. Thus, this current review gives complete detail of the analytical methods available on Indacaterol Maleate which can be helpful for further research work studies on it.

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