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A novel spectroscopic analysis to detect photochemical reaction of the bronchodilator – Doxofylline and its estimation in pharmaceutical formulation

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ABSTRACT

Photostability studies of drugs and drug products are an integral part of the product development process in the pharmaceutical industry. These studies are carried out to ensure quality, efficacy and safety of the formulated products during manufacture, storage and use. In this investigation, a novel spectroscopic approach has been adopted by employing the FTIR-ATR and UV/Visible techniques to detect the photochemical reactions of the drug Doxofylline, chemically designated as 7-(1, 3 dioxolane-2-*yl* methyl) theophylline, in its raw (pure) form. Significant changes were observed in terms of optical density of the absorption bands and a satisfactory analysis has been performed using ANOVA Statistics. It highlights the role of the photochemistry of drugs with respect to its spectral profiles and also explains photo physical processes. In addition; the drug compatibility study was also undertaken by using FTIR-ATR technique which indicated that there were no interactions occurring between the raw sample of the drug and the excipients used in the preparation of the pharmaceutical formulation. With this, UV–visible spectroscopic method was validated for the quantitative estimation of Doxofylline in pharmaceutical dosage forms and was performed with λ_{max} at 274 nm. Calibration curves were linear between the concentration range 10–50 μg/ml. The various parameters such as linearity, precision, accuracy, recovery and specificity were studied according to ICH guidelines (Ahmed et al., 2016; Jain et al., 2011; ICH, 1996).

1. Introduction

Doxofylline (DF) chemically designated as 7-(1, 3 dioxolane-2-*yl* methyl) theophylline and the presence of a dioxolane group in position C – 7 differentiates it from theophylline. It is a bronchodilator that plays a direct role in bronchial relaxation of bronchial smooth muscle. Its mechanism of action is related to the inhibition of phosphodiesterase within the smooth muscle cells and cause muscle relaxation, thus achieving suppression of asthma. However, differently from theophylline, Doxofylline appears to have decreased affinities towards adenosine A1 & A2 receptors which may account for the better safety profile of the drug. As per pharmacokinetic parameters the drug – Doxofylline is absorbed rapidly by the blood stream and hence the drug gets widely distributed in various organs, with high content in the lungs [4].

Apart from the activity of the drug, its photochemical reactions cannot be neglected as directions are given on the package of the drug not to expose the medicine to direct sunlight in order to avoid photochemical reactions which may degrade it even before its expiry time (Fig. 1).

The time necessary for the occurrence of a photochemical reaction is very short, so the possibility of a photochemical reaction of a drug due to various hazardous environment during the consuming process cannot be neglected, since the radiations from the sun or from a UV lamp can penetrate into the skin and can cause photochemical reactions on the medicine present in the blood circulation through exposed blood vessels. So, a thorough knowledge of possible reactions of the various exposed environment on the drug will be helpful in taking necessary precautions during its usage [5]. In the present work an attempt has been done to study the photochemical reactions of the Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline] and a method for its estimation pharmaceutical formulation with good accuracy, simplicity and precision has been adopted.

2. Materials and Methods

2.1. Instrumentation

FTIR-ATR, FT-Raman, UV–visible spectrophotometers, digital balance, micropipette and etc., were employed in the present study.

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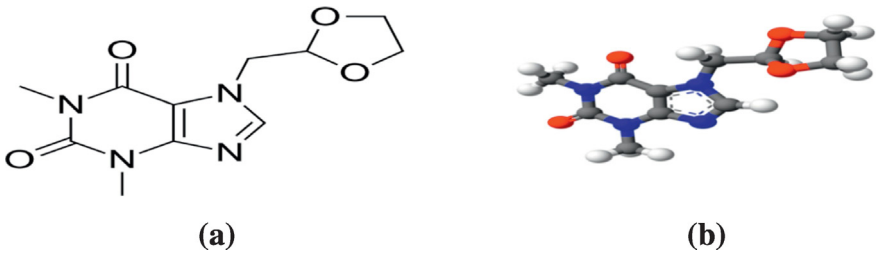

Fig. 1. (a) & (b) Chemical structure of Doxofylline.

2.2. Materials

Analytically pure (raw) samples of Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline] were procured as gift samples from Surien Pharmaceuticals Limited, Chennai, India. The obtained Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline], was having 99.99% w/w assay value and was used without further purification [6]. The pharmaceutical dosage form used in this study was T. Synasma (Ranbaxy Pharmaceuticals Ltd., Mumbai) containing 400 mg of Doxofylline, which was purchased from the local market. The total weight of a single T. Synasma was 533 mg out of this total weight 400 mg was the active substance, the raw material Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline]. The remaining 133 mg was due to the inactive ingredients such as corn (maize) starch, microcrystalline cellulose, povidone polyvinylpyrrolidone, which are the non-medicinal components, used in the dosage forms that has no therapeutic effect on the body, they are important and necessary components as these act as binding agents, preservatives, responsible for drug's shape, size & color and finally, used as disintegrants, helping the drug break up at the right time.

2.3. Methods

2.3.1. FTIR-ATR and FT-Raman Spectroscopic Techniques

The spectral measurements of drug samples with FTIR-ATR spectroscopy were carried out at SAIF – St. Peter's University, Chennai-54, using Perkin-Elmer Spectrum Two FTIR/ATR spectrophotometer. Each spectrum was measured in 4000–450 cm^{-1} range with a 4 cm^{-1} resolution and with 16 scans. All the samples were investigated by placing it on the crystal of 2 mm surface area with single bounce reflection has 350 cm^{-1} as its cutoff wave number; suitable pressure of about 140 N was given to the sample to make good optical contact between the sample and the internal reflectance element (IRE) the diamond. These spectra were subtracted against the background of air spectrum. After every scan, the crystal is cleaned with isopropyl alcohol or methanol soaked tissue and a background of new reference air was taken to ensure the crystal cleanliness. The spectra were constructed using the software 'Spectrum', provided with FTIR Spectrum Two Spectrophotometer [7]. The FT – Raman spectral measurement for the drug Doxofylline was carried out in the region 4000–50 cm^{-1} using Nd: YAG Laser 1064 nm operating at 200 mW on BRUKER RFS 27: stand alone FT – Raman spectrometer with multi RAM model of resolution 2 cm^{-1}, at SAIF - IIT, Chennai, India.

2.3.2. UV/Visible Spectroscopic Technique

2.3.2.1. Preparation of Standard Stock Solution. 100 mg of raw material of Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline] was weighed and transferred to 100 ml volumetric flask, then made the volume up to the mark with distilled water and the final concentration of the stock solution containing 1000 μg/ml of Doxofylline was prepared.

2.3.2.2. Preparation of Working Solution. Working standard solutions were prepared by taking dilutions ranging from 10 to 50 μg/ml of Doxofylline [7-(1, 3 dioxolane-2-*yl* methyl) theophylline] [8].

2.3.2.3. Selection of Detection Wavelength. Solutions of the drug were scanned over the range of 200–400 nm. It was observed that the drug showed considerable absorbance at 274 nm and was selected as the

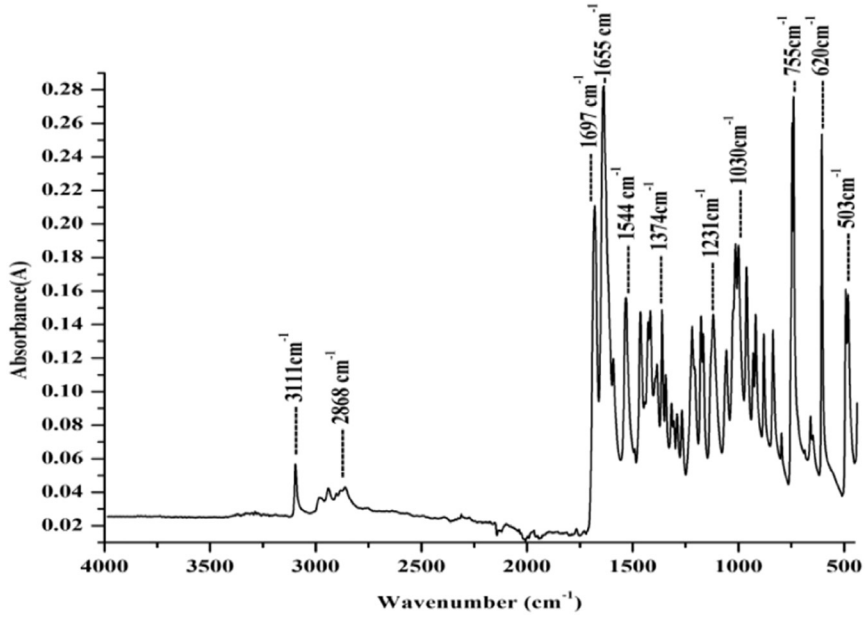

Fig. 2. FTIR-ATR spectrum of Doxofylline (raw form).