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ORIGINAL ARTICLE

Liquid chromatography and tandem mass spectrometry method for quantitative determination of pioglitazone and its metabolite 5-hydroxy pioglitazone in human plasma

Méthode de détermination quantitative, rapide et sensible, par chromatographie liquide et spectrométrie de masse en tandem de la pioglitazone et son métabolite, 5-hydroxy pioglitazone, dans le plasma humain

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KEYWORDS
LCMS;
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Summary A liquid chromatography tandem mass spectrometry (LC-MS/MS) based method was developed for the simultaneous estimation of pioglitazone and its active metabolites in human plasma for applicability to pharmacokinetic studies. The chromatographic separation was carried on the reversed phase Peerless Basic C18, column (100 × 4.6 mm, 5 μm) at column temperature of 40 °C using a binary mobile phase consisting of methanol: 5 mM ammonium acetate in 0.1% formic acid (80:20, v/v). The mobile phase was run at a flow rate of 1 mL/min and the sample injection was 10 μL. The method utilized pioglitazone D4 (IS1) and 5-hydroxyl pioglitazone M-IV D4 (IS2) as an internal standard. The linearity of the method was validated

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over the range of 6.04—1503.21 ng/mL for pioglitazone and 6.01—1496.28 ng/mL for 5-hydroxyl pioglitazone. The mean extraction recovery of PIO & HPIO from the spiked plasma was found to be 94.92% for pioglitazone and 96.13% for 5-hydroxy pioglitazone. The developed method can be successfully employed in healthy human volunteers to monitor the pharmacokinetics profile of pioglitazone.

MOTS CLÉS
LC-MS ;
Pioglitazone ;
LC-MS validation ;
Hydroxypioglitazone

Résumé Une méthode par chromatographie tandem liquide-spectrométrie de masse (LC-MS/MS) a été développée pour l'estimation simultanée de la pioglitazone (PIO) et de ses métabolites actifs dans le plasma humain pour l'application à des études pharmacocinétiques. La séparation chromatographique a été réalisée sur la phase inverse *Peerless Basic C18* avec une colonne (100 × 4,6 mm, 5 μm) à une température de colonne de 40 °C, en utilisant une phase mobile binaire méthanol : acétate d'ammonium 5 mM dans de l'acide formique à 0,1 % (80:20, v/v). La séparation a été effectuée à un débit de 1 mL/min et l'injection de l'échantillon était de 10 μL. La pioglitazone D4 (IS1) et 5-hydroxy pioglitazone M-IV D4 (IS2) ont été utilisées comme étalons internes. La linéarité de la méthode a été validée sur la plage de 6,04—1503,21 ng/mL pour la pioglitazone et 6,01 à 1496,28 ng/mL pour l'hydroxy pioglitazone (HPIO). Les coefficients moyens d'extraction dans du plasma additionné ont été de 94,92 % pour la PIO et 96,13 % pour la HPIO. La méthode développée peut être utilisée avec succès chez des volontaires humains sains pour étudier le profil pharmacocinétique de la pioglitazone.

Background

Pioglitazone hydrochloride is a thiazolidinedione derivative [1—3] with oral anti-hyperglycaemic activity used in the treatment of type 2 diabetes mellitus. Chemically is a thiazolidinedione derivative with an IUPAC name (±)-5-{4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl}-2,4-thiazolidinedione hydrochloride. The chemical structure of pioglitazone and 5-hydroxy pioglitazone is shown in Fig. 1. It shows hypoglycaemic effect by binding to PPARγ (peroxisome proliferator activated receptors gamma) and thus by increasing the insulin sensitivity in liver results in increases insulin dependent glucose disposal and decreased liver glucose output. It controls the glucose and lipid metabolism in the muscle, liver and adipose tissue by modulating the transcription of insulin sensitive genes [4—6].

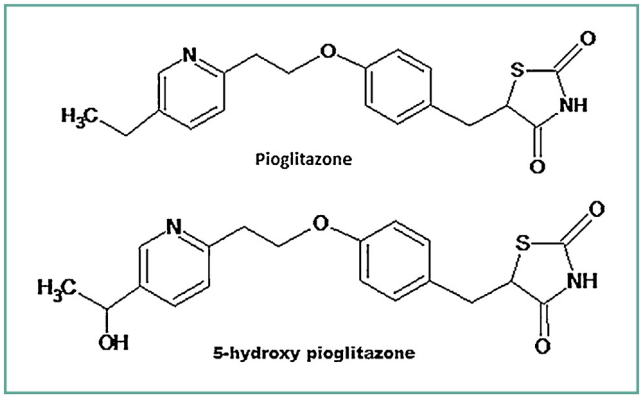

Figure 1. Chemical structures of pioglitazone and 5-hydroxy pioglitazone.
Structures chimiques de la pioglitazone et de la 5-hydroxy pioglitazone.

In the present study, estimation of pioglitazone and its metabolites 5-hydroxypioglitazone in human plasma (Fig. 1) were presented using LCMS-MS method. According to literature survey, a few analytical methods such as HPLC [7—9], HPTLC [10] and LCMS/MS [11,12] were reported for quantification of pioglitazone in pharmaceutical dosage form and in biological fluids as well. However, LCMS/MS method is very important method for determining drugs in biological samples such as plasma, serum, urine and other fluids.

Experimental

Material and methods

Pioglitazone hydrochloride, hydroxyl pioglitazone M-IV, pioglitazone D4 were obtained from Vivans Life Sciences Pvt. Ltd India. Hydroxyl pioglitazone M-IV D4- was purchased from Clearsynth Labs Limited, Mumbai, India. Ammonium acetate, dimethyl sulfoxide and formic acid were obtained from Merck (Bangalore, India). Methanol HPLC grade obtained from JT Barker (Gurgaon, India). HPLC grade water was obtained from RANKEM (India) and Strata-X 33 μM Polymeric sorbent were obtained from Phenomenex.

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