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Enhanced LC–MS/MS analysis of alogliptin and pioglitazone in human plasma: Applied to a preliminary pharmacokinetic study

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A B S T R A C T

A new fast LC–MS/MS method was developed for determination of alogliptin and pioglitazone in human plasma. Linearity ranges of 10–400 ng mL^{-1} for alogliptin and 25–2000 ng mL^{-1} for pioglitazone, were found to be suitable for their bioanalysis covering the C_{min} and C_{max} values of the drugs. Direct precipitation technique was used for simultaneous extraction of the drugs successfully from human plasma samples. Chromatographic separation was achieved on a BEH C_{18} column (50 mm × 2.1 mm, 1.7 μm) with 0.1% aqueous formic acid: acetonitrile (40:60, *v/v*) at a flow rate of 0.3 mL min^{-1}. The validated method was applied to a preliminary pharmacokinetic study on human volunteers. Monitoring the transition pairs of *m/z* 340.18 to 116.08 for alogliptin and *m/z* 356.99 to 133.92 for pioglitazone, using triple quadrupole mass spectrometer with multiple reaction monitoring, was achieved in the positive mode. The validated method is accurate and suitable for further clinical applications and possible bioequivalence studies.

1. Introduction

The effectiveness of a combined anti-diabetic treatment using both alogliptin (AG) and pioglitazone (PG) is better than single therapy and does not change their safety profile [1]. AG, (Fig. 1a), is an inhibitor to dipeptidyl peptidase-4 (DPP-4) that stimulates insulin release. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP) which inhibit glucagon release, which in turn increases insulin secretion and decreases blood glucose levels [1]. PG, (Fig. 1b), improves glycaemic control through its action at peroxisome proliferator-activated receptors (PPARs) increasing glucose utilization in the peripheral organs [2].

Many LC methods were reported for determination of AG [3–12] and PG [13–22]. Although some pharmacokinetic studies based on human subjects were reported for AG [23–25] and PG [26,27,18,28–31], only one pharmacokinetic study [1] considered AG combination with PG without full details regarding the used analytical procedures. Therefore, the novelty of the present work was achieved as the first described analytical procedure for the simultaneous extraction and LC–MS/MS determination of AG and PG accompanied with a preliminary pharmacokinetic study of the investigated drugs on healthy Egyptian volunteers as pharmacokinetic parameters can vary between different races. Literature review showed that a reported LC–MS/MS method was developed for simultaneous determination of AG and PG in river water [32]. Metformin (MT) was chosen as internal standard (IS) in the present work because of its similar behavior towards the proposed extraction procedure, low cost, availability and possible application to further clinical studies with gliptins or glitazones.

2. Experimental

2.1. Instrumentation

Waters Acquity UPLCH Xevo TQD system (USA) coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer and BEH C_{18} column with dimensions (50 mm × 2.1 mm, 1.7 μm) were used. Mass Lynx software version 4.1 was used. Validated Excel software was used to calculate the pharmacokinetic parameters.

2.2. Reagents and reference samples

Pharmaceutical grade AG and PG reference samples that certified to be 99.70% and 99.80%, respectively and Oseni® tablets (34 mg AG and 33.06 mg PG) were supplied by Takeda pharmaceutical company (Japan). Metformin (MT) reference sample that was certified to be 100.21%, was supplied from Chemical Industries Development (Egypt). HPLC grade acetonitrile was obtained from Fisher Scientific (UK). Formic acid was purchased from Sigma Aldrich (Germany).

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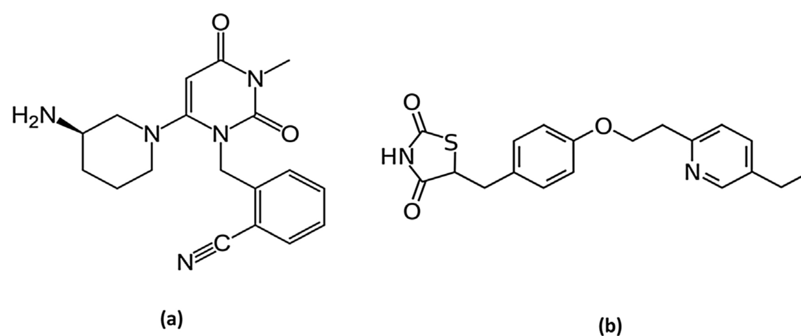

Fig. 1. Chemical structures of AG (a) and PG (b).

2.3. Working solutions

Working solutions of AG (20 μg mL^{-1}), PG (100 μg mL^{-1}) and MT (100 μg mL^{-1}) were prepared separately in methanol by appropriate dilution of the stock solutions (1 mg mL^{-1}) prepared in methanol.

2.4. Chromatographic conditions and mass detection parameters

A mixture of 0.1% aqueous formic acid and acetonitrile in the ratio of (40:60, *v/v*) was used keeping column temperature at 25 °C, using 10 μL as the injection volume and 0.3 mL min^{-1} as the flow rate. Cone voltage was set at 30 V while collision energy was set at 20 eV for both drugs monitoring the transition pairs of *m/z* 340.18 to 116.08, *m/z* 356.99 to 133.92 and *m/z* 130.06 to 71.14 for AG, PG and MT, respectively in the positive mode.

2.5. Sample preparation

Each AG and PG plasma sample (1 mL) was spiked with 10 μL of MT (IS, 100 μg mL^{-1}), extracted using 2 mL of previously prepared acetonitrile/0.1% perchloric acid mixture in the ratio of (99:1, *v/v*), vortexed for 1 min, centrifuged (3000 rpm) for 10 min and the supernatant was separated.

2.6. Procedure and method validation

2.6.1. Linearity

Concentrations equivalent to (0.4, 2, 4, 8, 12, 16 μg mL^{-1} AG) and (1, 10, 20, 40, 60, 80 μg mL^{-1} PG) were prepared in methanol using appropriate volumes of working solutions. Plasma samples were prepared by spiking of 950 μL human plasma with 25 μL of each AG and PG and finally spiked with 10 μL of IS (100 μg mL^{-1} MT). After repeating the extraction procedure mentioned under (sample prepara-

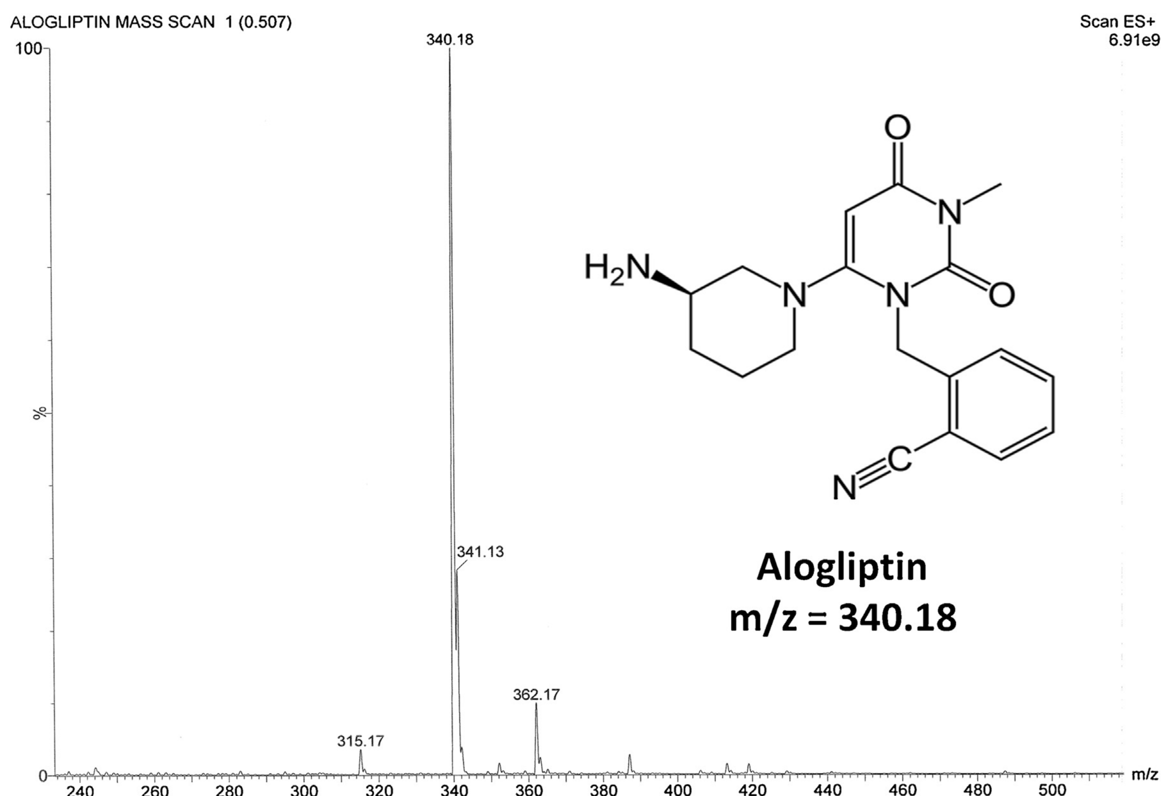

Fig. 2. Full scan mass spectrum of AG in positive ESI ion detection mode showing the parent ion.

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