AM-p-22

Glass catalysed conversion of candesartan cilexetil to the active metabolite candesartan and its alkylated derivates

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AIM: Candesartan cilexetil is an angiotensin II receptor antagonist (ARA II) widely used in the treatment of high blood pressure. This prodrug is metabolized into candesartan, which blocks the receptors AT1 for angiotensin II decreasing the blood pressure levels. During the development of a SPE-HPLC-ESI-MS/MS method to determine eight ARA II compounds, lack of linearity and reproducibility was observed for candesartan cilexetil. For understanding this effect, a stability study for this drug in methanolic solutions was developed.

METHODS AND RESULTS: Methanolic solutions of the drug (20 µg/mL) were heated at 60°C for 24 hours in glass tubes. No degradation of candesartan cilexetil could be observed. However, when these solutions were dried under nitrogen at 60°C, reconstituted and injected onto the chromatographic system (with DAD and ESI-MS/MS detection, Q1 scan mode), two new compounds were found besides candesartan cilexetil: candesartan and a methyl derivative of candesartan. To study the different variables which could affect the hydrolysis and transesterification, the same procedure was performed using plastic tubes and acetonitrile as solvent (with glass and plastic tubes), but no degradation was observed in these cases. The use of ethylene glycol to avoid total evaporation of solvent and irreversible adsorption of the analyte to the glass tubes has been described before for HPLC-analysis of drugs. To test these conditions, 100 µL ethylene glycol were added to the methanolic solution (900 µL) of candersartan cilexetil before evaporation of the volatile content – with the ethylene glycol remaining in the glass tube. In this case, two compounds as well as candesartan cilexetil were detected: candesartan and a hydroxylethyl derivative of candesartan. When the whole procedure was repeated with a new lot of glass tubes, only very small amounts of candesartan and its derivatives were observed. The new glass tubes were then washed with acidic and basic solutions, respectively, prior to rinsing them with deionised water. With the basic conditioned glass tubes, hydrolysis and transesterification were observed, after washing with the acidic solution the prodrug was stable.

CONCLUSIONS: The formation of candesartan and its esters can be explained as a basic hydrolysis of candesartan cilexetil and a transesterification reaction of the prodrug catalyzed by the surface of glass tubes, due to any kind of basic contamination in the tubes. It was found that differences between using different lots of glass and even glass tubes from the same lot were noticeable. We recommend checking these phenomena whenever esters or other labile drugs are analysed.

KEYWORDS: *Stability, hydrolysis, Esterification*

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