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Identification of the major degradation pathways of ticagrelor

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ABSTRACT

Ticagrelor is a direct-acting and reversible $P2Y_{12}$-adenosine diphosphate (ADP) receptor blocker used as antiplatelet drug. Forced degradation under various stress conditions was carried out. The degradation products have been detected and identified by high-pressure liquid chromatography multistage mass spectrometry (LC-MS^n) along with high-resolution mass spectrometry. C_{18} XTerra MS column combined with a linear gradient mobile phase composed of a mixture of 10 mM acetate ammonium/acetonitrile was shown suitable for drug and impurity determinations and validated as a stability indicating method. Structural elucidation of the degradation products relied on MS^n studies and accurate mass measurements giving access to elemental compositions. Up to nine degradation products resulting from oxidation/auto-oxidation, S-dealkylation and N-dealkylation have been identified, covering a range of possible degradation pathways for derivatives with such functional groups. Kinetics was also studied in order to assess the molecule's shelf-life and to identify the most important degradation factors.

1. Introduction

Ticagrelor, (1S,2S)-3-[7-[[(1R,2S)-2-(3,4-difluorophényl)cyclopropyl]amino]-5-propylsulfanyltriazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyéthoxy)cyclopentane-1,2-diol is a new antiplatelet agent, the first reversible P2Y12-adenosine diphosphate (ADP) receptor blocker indicated in the treatment of acute coronary syndromes (ACS) [1,2]. Until recently, clopidogrel was the key P2Y12 antagonist advocated, but recent large-scale randomized trials have demonstrated net clinical benefit of the new antiplatelet agents (ticagrelor and prasugrel) with respect to clopidogrel [2,3]. Therefore, the European guidelines recommend ticagrelor and prasugrel as first-line treatment in patients presenting with non-ST segment elevation ACS and ST-segment elevation ACS [4,5]. Ticagrelor provides fast, great and more consistent ADP-receptor inhibition.

Even properly designed, marketed drugs undergo environmental stresses, which may result in a loss of activity and cause adverse effects owing to the advent of degradation products. One of the best ways to apprehend the phenomenon and to anticipate risks is to get access to degradation pathways in order to determine intrinsic stability of drugs, according to ICH recommendations [6]. LC-MS^n in conjunction with accurate mass measurements has been increasingly used for structural characterization of degradation products [7]. The literature shows scant information on stability and degradation behaviour of ticagrelor. Its metabolites have been described in plasma using hyphenated LC-MS [8,9]. An LC stability indicating method was developed to determine ticagrelor in presence of its degradation products, but structural elucidation was not described [10].

The pharmaceutical importance of ticagrelor as an antiplatelet drug has prompted us to carry out a characterization study of its degradation products generated under harsh conditions, by using LC–MS^n along with high-resolution MS. A stability indicating method intended to drug quantification and impurity determination was also developed and validated. Kinetics was

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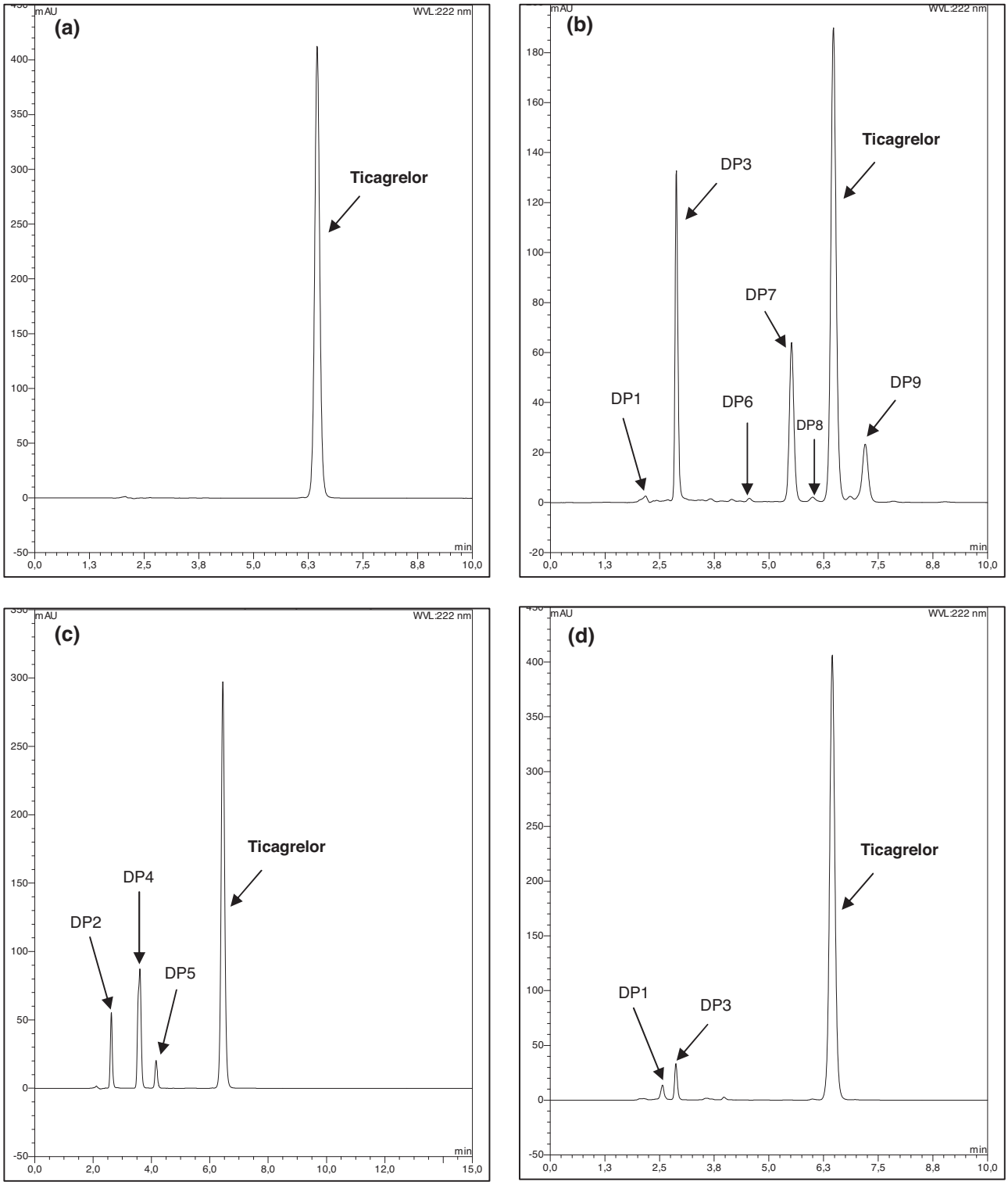

Fig. 1. LC–UV chromatograms resulting from exposition to tested stress factors: (a) ticagrelor standard solution; (b) photolytic condition; (c) oxidation condition; (d) thermal stress condition.