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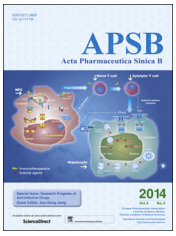

ORIGINAL ARTICLE

Characterization of impurities in cefpodoxime proxetil using LC–MS^n

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KEY WORDS

Cefpodoxime proxetil;
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Structure identification

Abstract Reversed-phase liquid chromatography coupled with electrospray ionization tandem mass spectrometry (ESI-MS/MS) was used to characterize impurities in cefpodoxime proxetil, an ester-modified prodrug. Based on the mechanisms by which cephalosporins are degraded, stress tests were designed and performed. The bulk material and capsule were eluted through a C18 column with formic acid–methanol–water as the mobile phase. In total, 15 impurities were characterized in commercial samples, including 7 known impurities and 8 new impurities. The structures of these unknown compounds were deduced *via* comparison with the fragmentation patterns of cefpodoxime proxetil. Data from this systematic study will help improve the safety and quality of cefpodoxime proxetil.

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1. Introduction

Cefpodoxime proxetil (Fig. 1), an ester-modified prodrug, is an oral, broad-spectrum third generation cephalosporin antibiotic[1]. It has *in vitro* activity against many common Gram-positive and Gram-negative pathogens associated with common pediatric infections, so it is a useful option for empirical therapy[2]. It is listed in the United States Pharmacopeia 36th Edition[3], the European Pharmacopeia 7.0 Edition[4] and the Japanese Pharmacopeia 15th Edition[5]. Different analysis methods have been developed[6,7] and compared[8] to measure impurities and degradation products. Fukutsu et al.[9] identified three degradation products of cefpodoxime proxetil by high-performance liquid chromatography-hyphenated techniques. However, ICH guidelines Q3A require that all impurities (from processing and degradation) be identified above a certain threshold[10]. Yet, at this time, a systematic study for identifying cefpodoxime proxetil impurities is not available. Hence, we focused on identifying unknown process impurities and degradation products in cefpodoxime proxetil using a chromatographic system from the European Pharmacopeia 7.0 Edition using liquid chromatography with diode array detection (LC-DAD), multiple stage mass spectrometry (MS^n), and liquid chromatography–high-resolution mass spectrometry (LC–HRMS) methods along with stress degradation tests, degradation[11–13] and mass fragmentation mechanisms of cephalosporins[14–16], and related synthesis processes[17,18]. These studies will inform future quality control and safety of cefpodoxime proxetil products. We characterized 15 impurities including 4 new degradation products and 4 new process impurities, along with 7 known impurities as identified in the European Pharmacopeia. We would discuss these as well as the most likely cause of their appearance and the mass fragmentation pathways of the impurities.

2. Materials and methods

2.1. Reagents and samples

HPLC-grade acetonitrile was purchased from Thermo Fisher Scientific (Fair Lawn, NJ). Formic acid (98.0%) was supplied by Sigma-Aldrich Co. Ltd. (St. Louis, MO, US) and analytical-grade hydrochloric acid (HCl), sodium hydroxide (NaOH) and hydrogen peroxide (H_2O_2, 30%) were obtained from Beijing Chemical Works

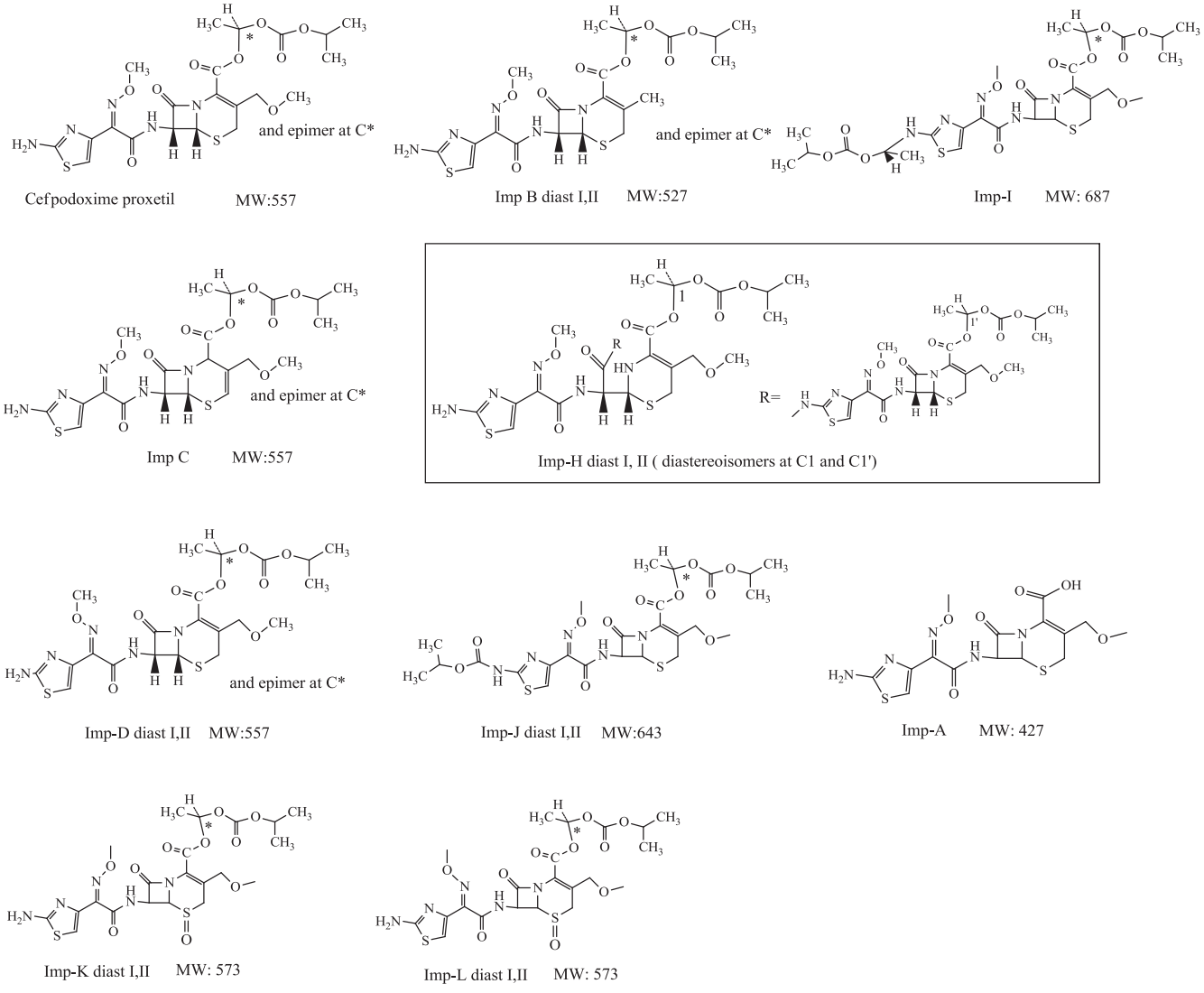

Figure 1 Proposed chemical structures of 15 impurities and cefpodoxime proxetil.