



Isolation, identification and characterization of potential impurities of anidulafungin



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ABSTRACT

Eight impurities ranging from 0.03 to 0.97% in anidulafungin bulk drug were detected by HPLC. Four impurities (Imp-I, Imp-II, Imp-III and Imp-VIII) among impurities were isolated from the self-prepared or marketed samples of anidulafungin bulk drug by means of preparative HPLC. A thorough study was undertaken to characterize these impurities and based on 1D (¹H, ¹³C, H-D, DEPT 90 and 135) and 2D (COSY, TOCSY, HSQC, HMBC) NMR and ESI-MS spectral data. Based on the characterization data, Imp-I was found to be known open-chain hydrolysis product formed during the synthesis and degradation. Imp-II and Imp-III was lacked a methyl group at the C-4 and C-8 in anidulafungin, respectively, whereas Imp-VIII contained a methoxy group at the C-23. The latter three new impurities were identified as process-related substances.

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1. Introduction

Anidulafungin is a novel antifungal agent and a member of the class of echinocandins. It is used to treat invasive fungal infection, such as *Candida* infection, *Aspergillus* infection and *Esophageal Candidiasis* infection [1–3]. The mechanism of action of anidulafungin is based upon noncompetitive inhibition of the (1, 3)-β-D-glucan synthase, an essential component of fungal cell walls [4]. Anidulafungin contains 6 amino acid fragments and the cyclic hexapeptide is N-linked to an alkoxytriphenyl side chain [5]. Anidulafungin is a semi-synthetic lipopeptide synthesized from echinocandin B (ECB), which is the fermentation produces of *Aspergillus nidulans*, through enzymatic deacylation of the linoleoyl side chain using an *Actinoplanes utahensis* culture to provide echinocandin B nucleus (ECBN), and subsequent the key intermediate is reacted with 1-([4''-(pentyloxy)-1,1':4',1''-terphenyl-4-yl]carbonyl)oxy-1H-1,2,3-benzotriazole (TOBT) in DMF by chemical reacylation at the N-terminus [6–9]. The synthetic route (Fig. 1) is widely reported and applied in laboratory sample preparation and commercial production. Impurities inevitably form at the end of this process, and include unreacted starting materials, by-products, intermediates, and degradation products. With ever increasing regulatory concerns on the quality and

safety of pharmaceuticals, a systematic investigation of impurities and degradation products in anidulafungin bulk drug is of paramount importance. The echinocandin B is the main component for synthesis anidulafungin, but during fermentation several related substances such as echinocandin C, D and A30912H are formed in small amounts [10]. So the starting material, echinocandin B, contains impurities which may react during the subsequent manufacture. In addition, degradation products such as open-chain hydrolysis product formed in alkaline medium and bis-terphenyl acid derivative formed by over-reaction, are also be present [11–14]. Several unknown impurities are observed by HPLC analysis at levels ranging from 0.03 to 0.97% (Fig. 2) in self-prepared sample of anidulafungin bulk drug from our laboratory and marketed sample of anidulafungin bulk drug purchased from Pfizer. However the identification and structure elucidation of potential impurities except open-chain hydrolysis product and bisterphenyl side product are not mentioned in the literature till date [14,15]. In addition, to the best of our knowledge, no studies concerning the characterization of process-related impurities have been reported so far. The impurities of anidulafungin are directly related to the development and commercialization of this bulk drug, because the stringent purity requirement that all the individual impurities, which are ≥ 0.1%, must be identified and characterized. In this study, the potential impurities of anidulafungin bulk drug are identification, isolation and characterization using high performance liquid chromatography. The structures of impurities are confirmed with support of spectral analysis such as 1D NMR (¹H, ¹³C, H-D

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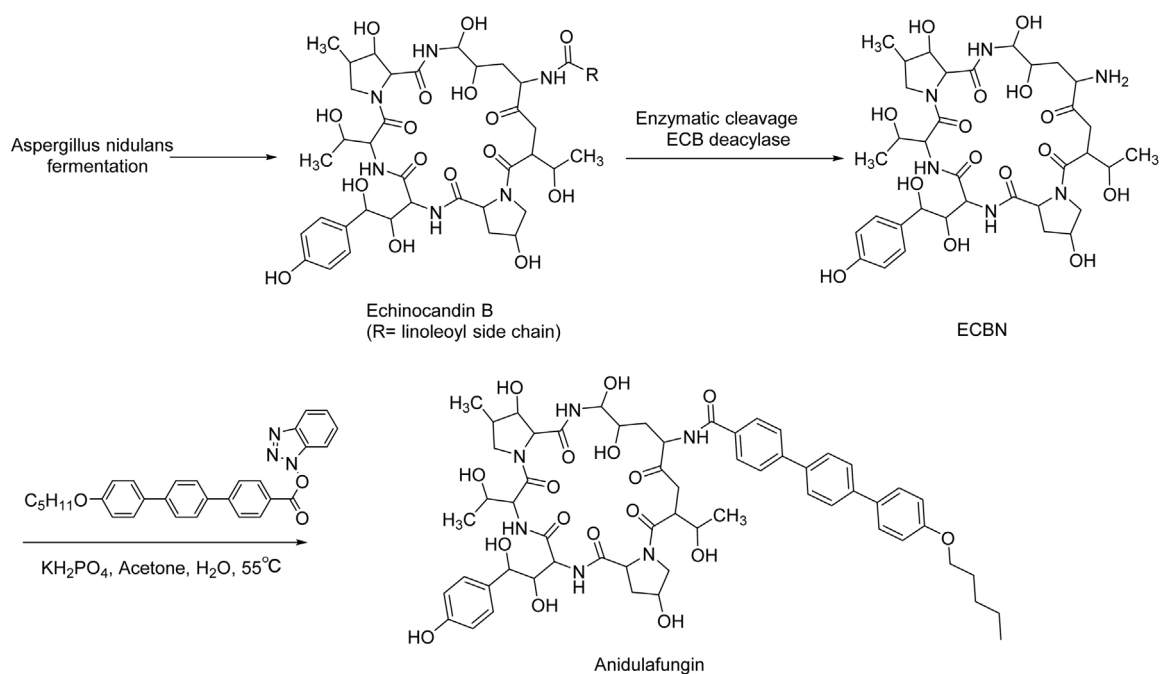


Fig. 1. The synthesis route of anidulafungin.

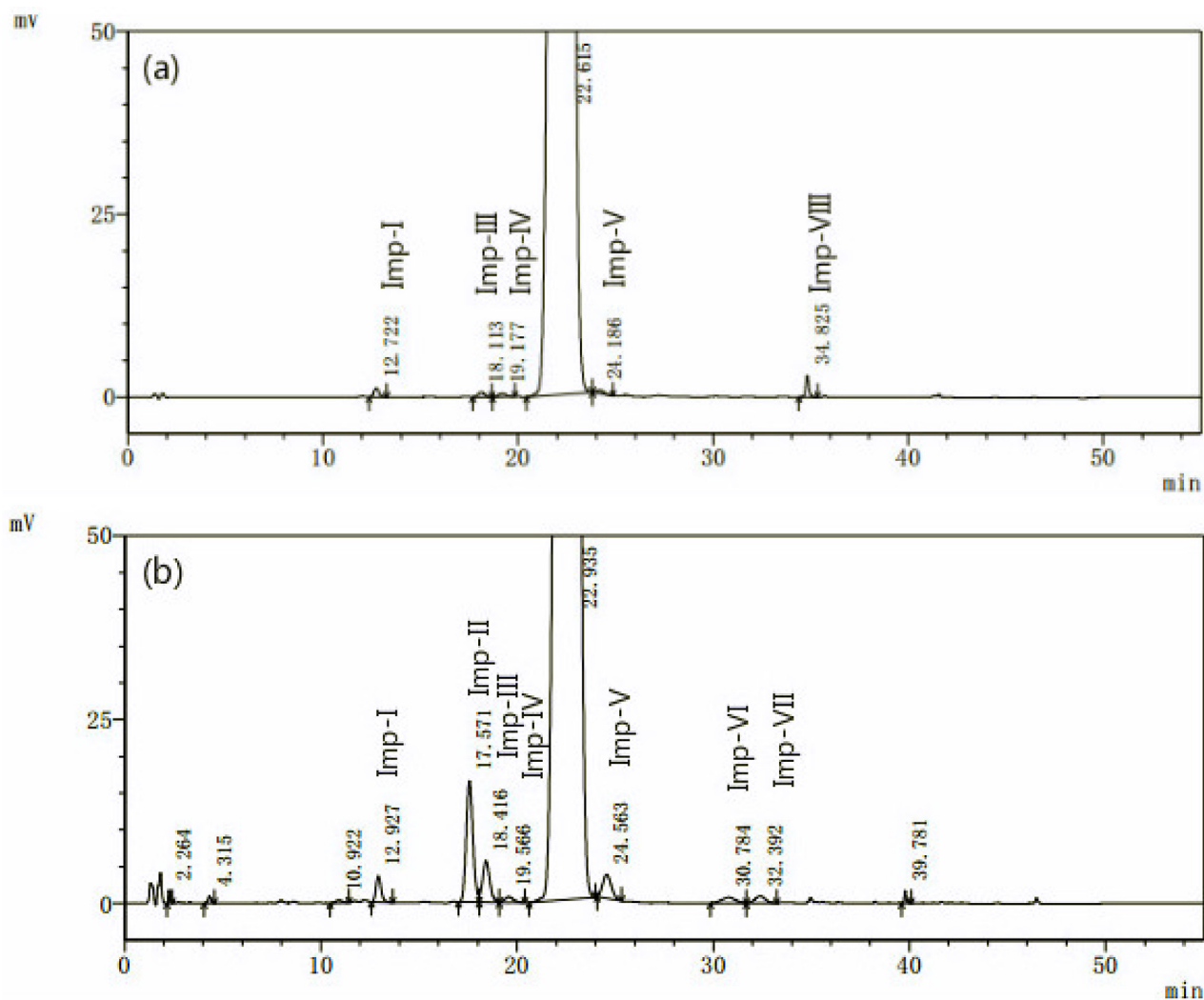


Fig. 2. HPLC chromatogram of (a) self-prepared samples of anidulafungin from our laboratory; (b) marketed sample of anidulafungin from Pfizer.

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