Synthesis and physicochemical characterization of the impurities and the key intermediate of pemetrexed disodium, an anticancer drug

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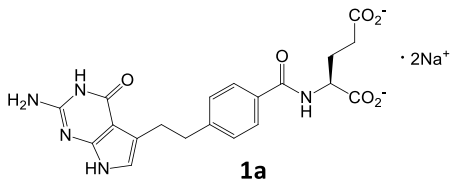
Pemetrexed (1a) is an antifolate antineoplastic agent that acts by inhibiting the formation of precursor purine and pyrimidine nucleotides. Pemetrexed prevents the formation of DNA and RNA, which are required for the growth and survival of both normal and cancer cells [1]. A pharmaceutical product containing pemetrexed disodium (Fig. 1) as the active ingredient is used for the treatment of malignant pleural mesothelioma (MPM) and metastatic non-small cell lung cancer (NSCLC) [2].



1a

Fig. 1. The structural formula of pemetrexed disodium.

The European Medicine Agency and the U.S. Food and Drug Administration require complete physicochemical characteristic not only for an active pharmaceutical ingredient, but also for its key synthetic intermediates and the impurities formed during synthesis drug products.

Therefore the development of the synthesis methods for impurities and new crystalline forms of pemetrexed diacid – a key intermediate of pemetrexed disodium was described. Physicochemical characterizations of impurities and pemetrexed diacid were performed by means of thermal analysis, spectroscopic methods and powder diffraction. Structures elucidation on the basis of two-dimensional NMR experiments were discussed in details [3, 4]. Additionally, in this work, the crystal structure of pemetreksed diacid form C [5] will be presented, together with its spectroscopic and thermal characteristics.

The identification of these impurities and the intermediate is essential for the quality control during the production of the pemetrexed disodium salt.

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