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Experimental and Theoretical Investigations of the Chemotherapeutic Drug Capecitabine

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ABSTRACT

Capecitabine (CAP) is a pro-drug of the anti-metabolites group, mainly used in treating breast, gastro-intenstinal and genito-urinary tracts cancers. In spite of the great number of studies reporting about its side-effects, pharmacokinetic and crystal structure investigations, there is a lack of data related to its structure and vibrational properties, as well as an analysis of its behavior at very low concentrations. Considering the complexity and the biological importance of this drug, we considered highly important to obtain a complete structural and vibrational characterization of the title compound. Such investigations could be the starting point for detecting and monitoring the compound in more complex systems like body fluids. Therefore, in this work, we present a joint experimental and theoretical analysis of CAP, using Raman and IR spectroscopic techniques coupled to DFT calculations, aiming to analyze the relative stability of its solid-state tautomers and to explain the vibrational features of the molecule. SERS measurements were also performed on CAP and obtained a very good signal even at low concentrations ($0.5 \cdot 10^{-4}$ M). SERS analysis along with the molecular electrostatic potential (MEP) map enabled us to conclude about the adsorption geometry and orientation of the molecules on the gold surface.

1. Introduction

Capecitabine (CAP), with the IUPAC name Pentyl [1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1*H*-pyrimidin-4-yl]carbamate, is a prodrug of 5-fluorouracil (5-FU) and the active substance in Xeloda® which belongs to the cytostatic group, a type of pharmaceuticals that inhibit cancer cell growth [1,2].

CAP is effective in treating breast, esophagus, larynx, gastro-intestinal and genito-urinary tracts cancers, and is also used in preventing the recurrence of colon cancer after the surgical removal of the tumor [1,3]. The compound is selectively tumor-activated, being dependent on enzymes, which have generally higher concentrations in tumor tissue than in healthy tissue. Its anti-metabolic activity starts as a result of it being converted to 5-fluorouacil (5-FU) by thymidine phosphorylase, which further interferes with the production of new DNA [2,4].

CAP was developed as an improvement to its active moiety 5-FU, which was initially administered intravenously, mainly as treatment for solid tumors [5]. The drug is designed to traverse the gastro-intestinal tract to reach the liver, causing no toxic effect along the way [6]. In order to metabolize to 5-FU, CAP passes through three sequential steps. Firstly, it is converted in the liver by carboxylesterase to 5-deoxy-5fluorocytidine, which is then converted by cytidine deaminase to 5-deoxy-5fluorouridine. Finally, 5-deoxy-5fluorouridine is converted to the active drug 5-FU by thymidine phosphorylase, which is up to 10 times more abundant in tumorous tissue than in healthy ones [6,7].

Considering the high cytotoxicity of this type of drugs, different patient metabolisms and other circumstantial factors for each treatment, it is essential to consider the importance of therapeutic drug monitoring (TDM) in treating cancer. Such data can help physicians to modify the dosage in order to obtain a more efficient treatment that is tailored for each patient [8]. Because of its high sensitivity and ability to detect analytes at low concentrations, Surface Enhanced Raman Spectroscopy (SERS) is an appropriate technique highly useful in identifying drugs at very low concentrations. Recently, there have been quite a few studies regarding the applicability of SERS in TDM [9–12] each one presenting a different approach.

Prior to performing SERS measurements it is necessary to obtain a complete vibrational characterization of the drugs in order

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